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=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 17:54:22 ON 02 DEC 2005
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FILE COVERS 1907 - 2 Dec 2005  VOL 143 ISS 24
FILE LAST UPDATED: 1 Dec 2005  (20051201/ED)

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 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

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L1                  STR
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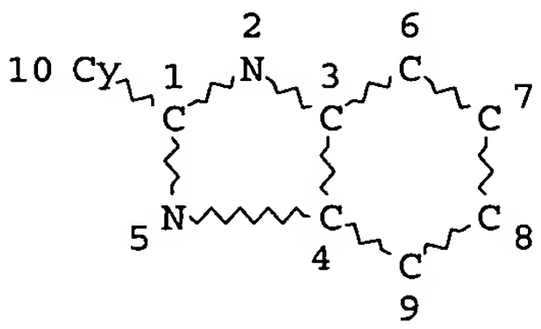


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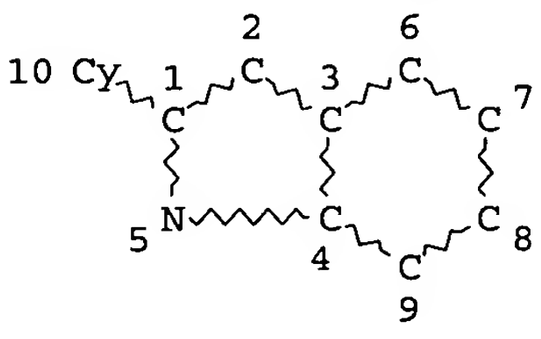


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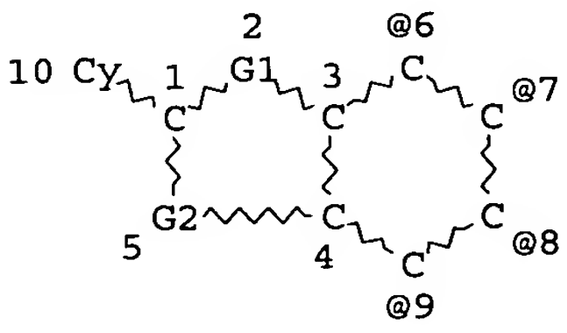

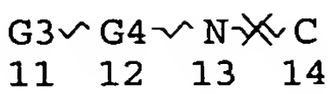

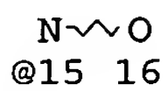

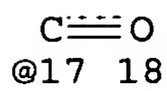

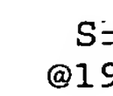

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VAR G4=17/19
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DEFAULT MLEVEL IS ATOM
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STEREO ATTRIBUTES: NONE
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=> d ibib abs hitstr l7 1-6

L7 ANSWER 1 OF 6 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:136530 HCAPLUS
DOCUMENT NUMBER: 142:233301
TITLE: Selective pharmacologic inhibition of protein trafficking and related methods of treating human diseases
INVENTOR(S): Sircar, Jagadish; Richards, Mark L.
PATENT ASSIGNEE(S): Avanir Pharmaceuticals, USA
SOURCE: PCT Int. Appl., 134 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005013950	A2	20050217	WO 2004-US26435	20040809
WO 2005013950	A3	20050901		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2005256179	A1	20051117	US 2004-915722	20040809
PRIORITY APPLN. INFO.:			US 2003-493497P P	20030808

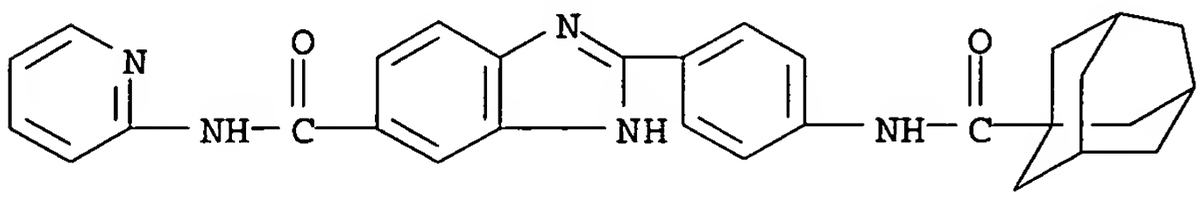
OTHER SOURCE(S): MARPAT 142:233301

AB Preferred aspects of the present invention relate to the inhibition of intracellular protein trafficking pathways through selective pharmacol. down-regulation of specific resident ER and golgi proteins, and more particularly, to methods of treating a variety of disease conditions, which depend on these intracellular protein trafficking pathways.

IT **459805-03-9 675823-17-3 675823-18-4 675823-19-5 675823-23-1**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(selective pharmacol. inhibition of protein trafficking and related methods of treating human diseases)

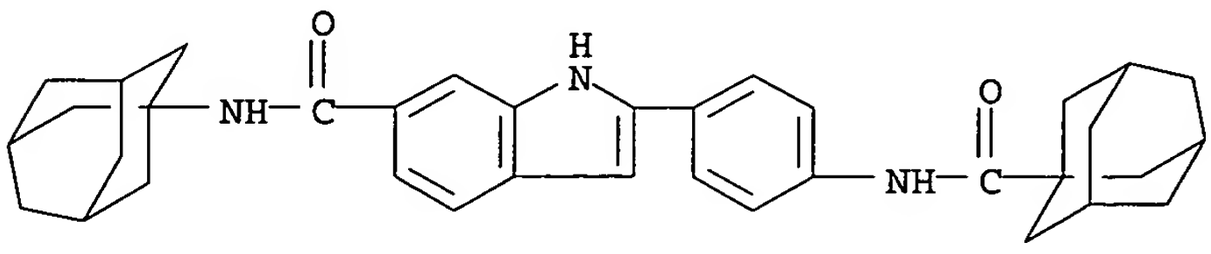
RN 459805-03-9 HCAPLUS

CN 1H-Benzimidazole-5-carboxamide, N-2-pyridinyl-2-[4-[(tricyclo[3.3.1.13,7]dec-1-ylcarbonyl)amino]phenyl]- (9CI) (CA INDEX NAME)



RN 675823-17-3 HCAPLUS

CN 1H-Indole-6-carboxamide, N-tricyclo[3.3.1.13,7]dec-1-yl-2-[4-[(tricyclo[3.3.1.13,7]dec-1-ylcarbonyl)amino]phenyl]- (9CI) (CA INDEX NAME)



RN 675823-18-4 HCAPLUS

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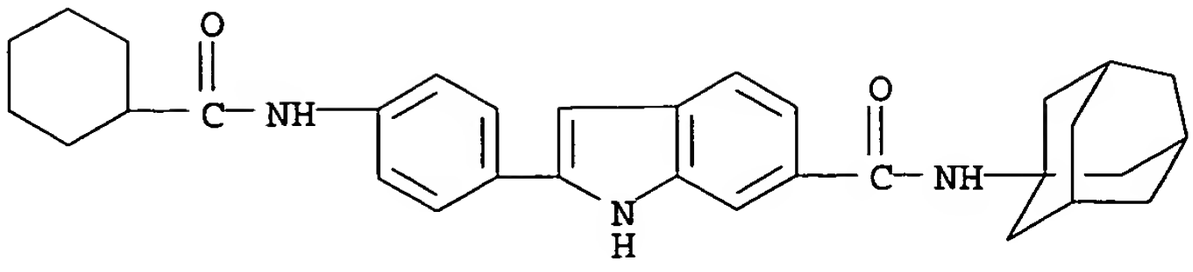
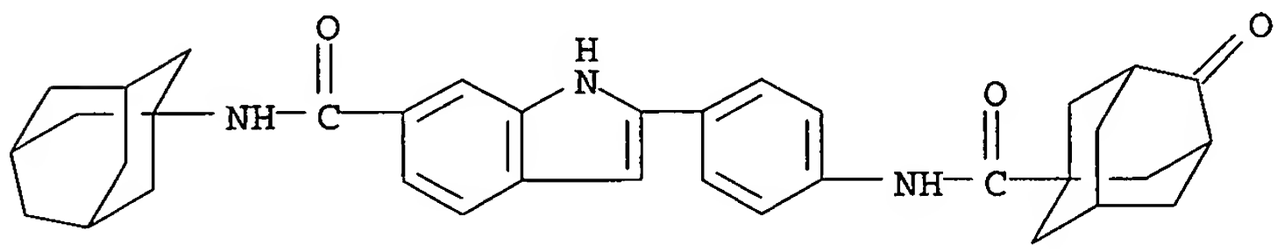
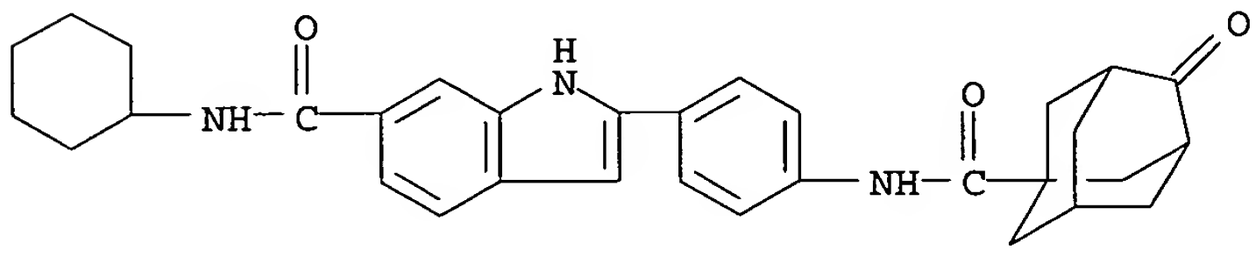


RN 675823-19-5 HCAPLUS
CN 1H-Indole-6-carboxamide, 2-[4-[[(4-oxotricyclo[3.3.1.13,7]dec-1-yl)carbonyl]amino]phenyl]-N-tricyclo[3.3.1.13,7]dec-1-yl- (9CI) (CA INDEX NAME)



RN 675823-23-1 HCAPLUS
CN 1H-Indole-6-carboxamide, N-cyclohexyl-2-[4-[[(4-oxotricyclo[3.3.1.13,7]dec-1-yl)carbonyl]amino]phenyl]- (9CI) (CA INDEX NAME)



L7 ANSWER 2 OF 6 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:220328 HCAPLUS
DOCUMENT NUMBER: 140:270869
TITLE: Preparation of pyrimidinylindolecarboxamides and pyrimidinylbenzimidazolecarboxamides as inhibitors of IκB kinase.
INVENTOR(S): Ritzeler, Olaf; Jaehne, Gerhard
PATENT ASSIGNEE(S): Aventis Pharma Deutschland GmbH, Germany
SOURCE: PCT Int. Appl., 56 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004022553	A1	20040318	WO 2003-EP8629	20030805

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN,

TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

DE 10237722	A1	20040819	DE 2002-10237722		20020817
CA 2498559	AA	20040318	CA 2003-2498559		20030805
EP 1530568	A1	20050518	EP 2003-793685		20030805
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US 2005197353	A1	20050908	US 2003-642970		20030818
PRIORITY APPLN. INFO.:			DE 2002-10237722	A	20020817
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			WO 2003-EP8629	W	20030805

OTHER SOURCE(S): MARPAT 140:270869
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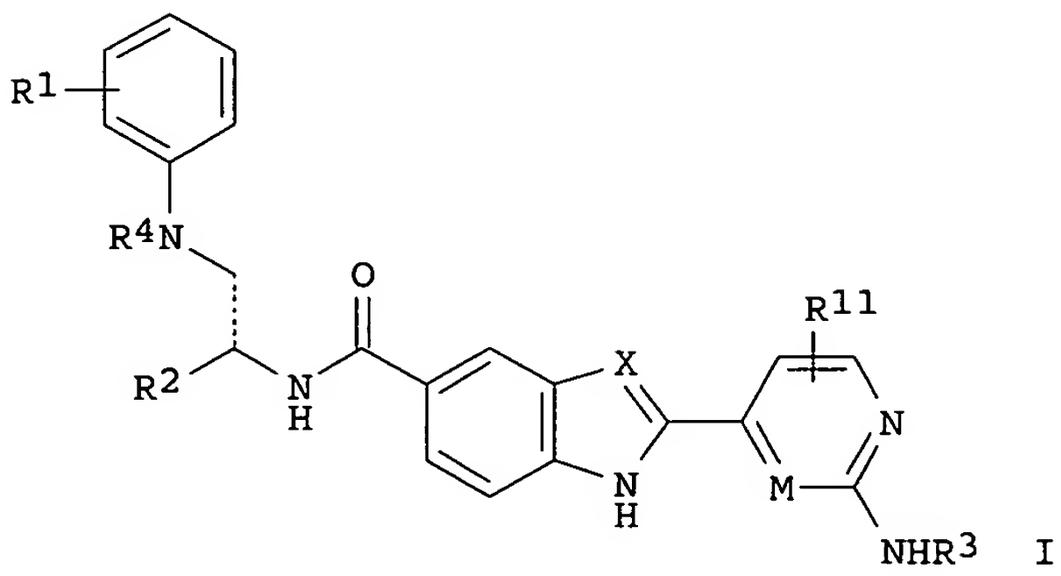


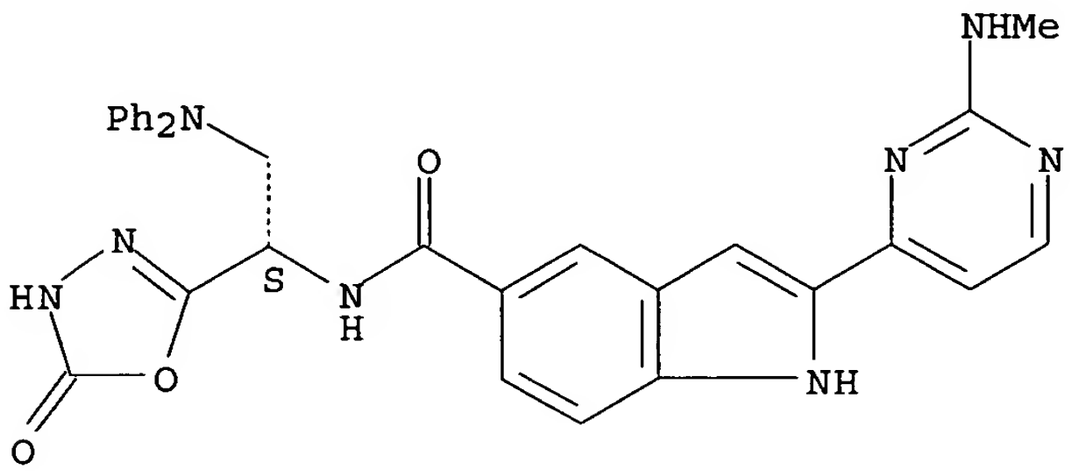
AB Title compds. [I; X, M = N, CH; R1, R11 = H, F, Cl, Br, iodo, alkyl, cyano, CF3, OR5, NR5R6, COR5, SOxR5, etc.; x = 0-2; R3, R5, R6 = H, alkyl; R2 = (substituted) imidazolyl, imidazolidinyl, indazolyl, isothiazolyl, isoxazolyl, morpholinyl, piperazinyl, pyrazolyl, tetrazolyl, thiadiazolyl, thiazolyl, thiomorpholinyl, triazolyl, etc.; R4 = (substituted) (fused) pyrrolyl, furyl, thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl, phthalazinyl, isoquinolinyl, quinoxalinyl, quinazolinyl, etc.], were prepared Thus, 2-(2-methylaminopyrimidin-4-yl)-1H-indole-5-carboxylic acid [(S)-2-diphenylamino-1-hydrazinocarbonylethyl]amide (preparation given) in CH2Cl2 was treated with phosgene followed by stirring for 15 h to give 76% 2-(2-methylaminopyrimidin-4-yl)-1H-indole-5-carboxylic acid [(S)-2-diphenylamino-1-(5-oxo-4,5-dihydro[1,3,4]-oxadiazol-2-yl)ethyl]amide. The latter inhibited IκB kinase with IC50 = 0.050 μM.

IT **669713-30-8P 669713-32-0P 673488-41-0P**
673488-42-1P 673488-43-2P 673488-44-3P
673488-45-4P 673488-46-5P 673488-47-6P
673488-48-7P 673488-49-8P 673488-50-1P
673488-51-2P 673488-52-3P 673488-53-4P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of pyrimidinylindolecarboxamides and

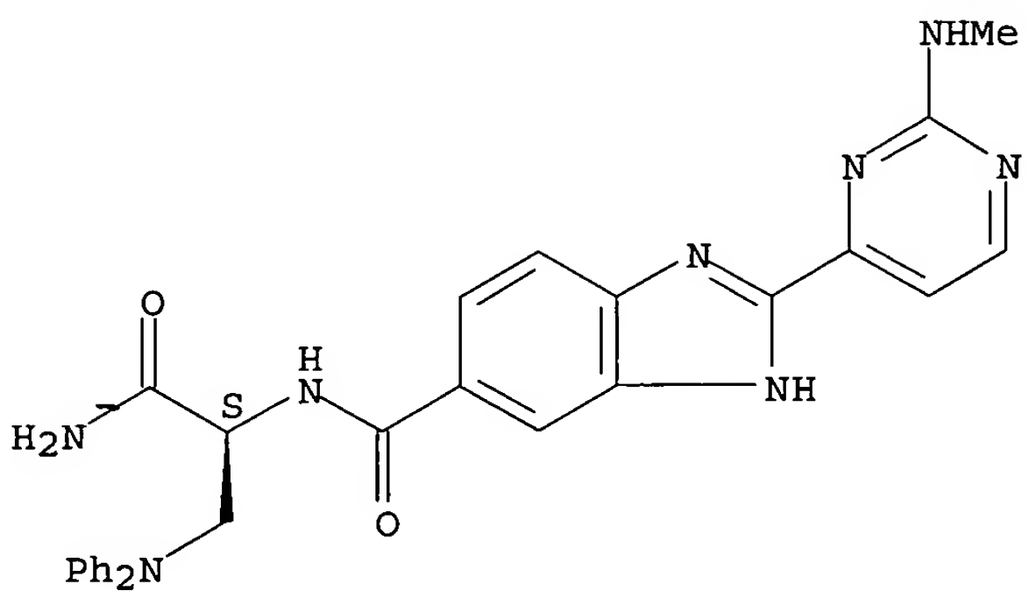
pyrimidinylbenzimidazolecarboxamides as inhibitors of IκB kinase)

RN 669713-30-8 HCAPLUS
CN 1H-Indole-5-carboxamide, N-[(1S)-1-(4,5-dihydro-5-oxo-1,3,4-oxadiazol-2-yl)-2-(diphenylamino)ethyl]-2-[2-(methylamino)-4-pyrimidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 673488-41-0 HCAPLUS
CN 1H-Indole-5-carboxamide, N-[2-amino-1-[[(4-fluorophenyl)-2-pyridinylamino]methyl]-2-oxoethyl]-2-[2-(methylamino)-4-pyrimidinyl]- (9CI) (CA INDEX NAME)



RN 673488-42-1 HCAPLUS
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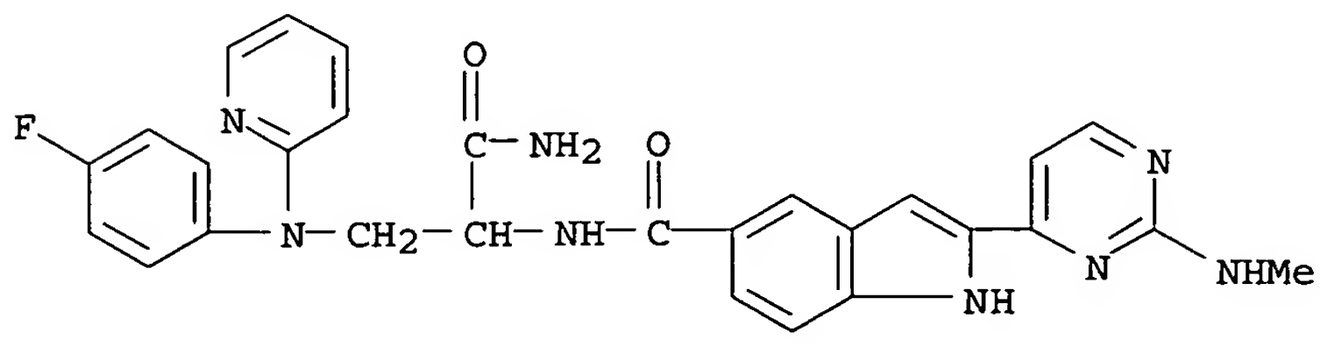

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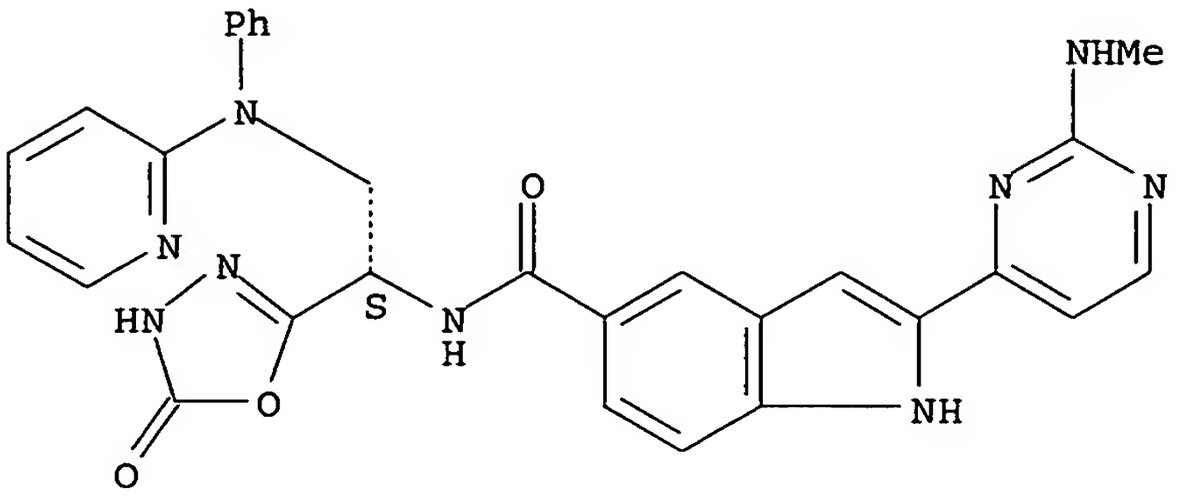
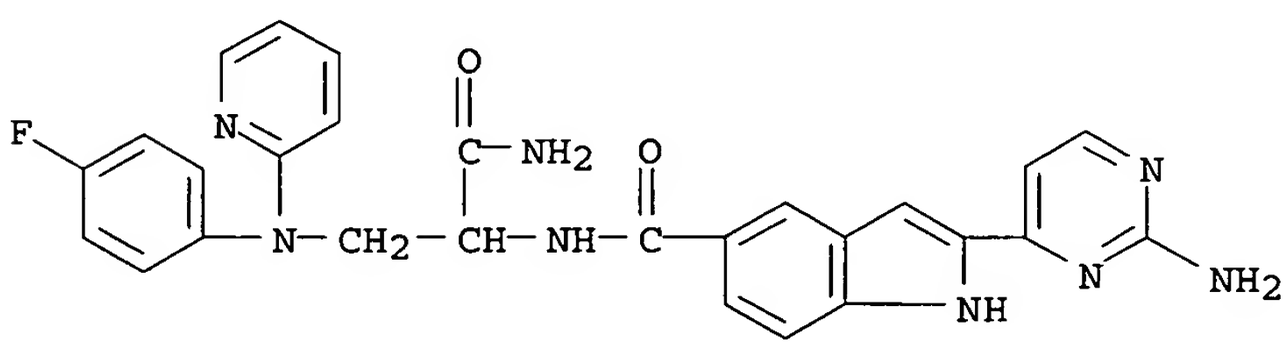
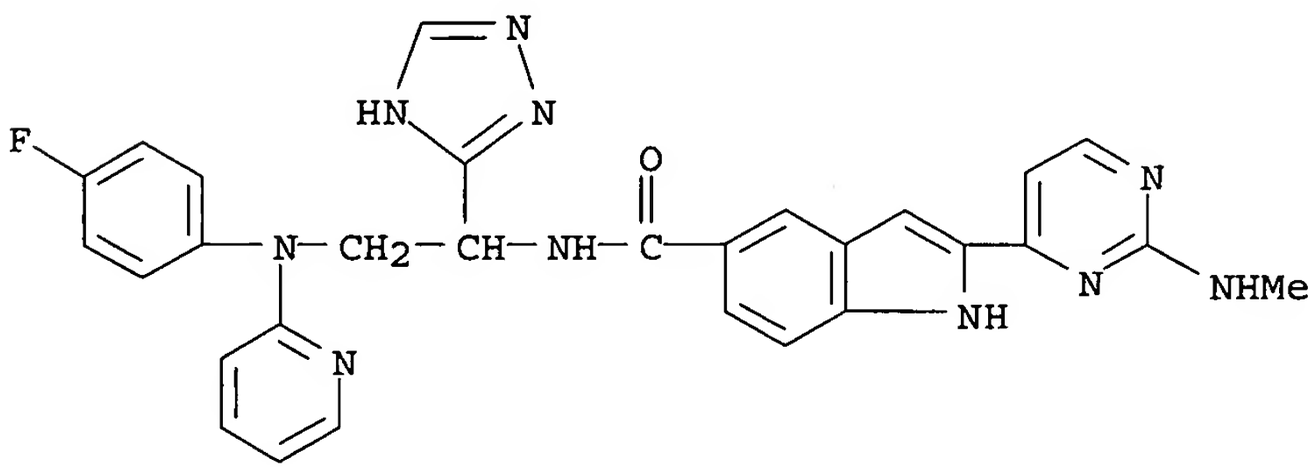
Absolute stereochemistry.



RN 673488-43-2 HCAPLUS
CN 1H-Indole-5-carboxamide, N-[2-amino-1-[[(4-fluorophenyl)-2-pyridinylamino]methyl]-2-oxoethyl]-2-(2-amino-4-pyrimidinyl)- (9CI) (CA INDEX NAME)

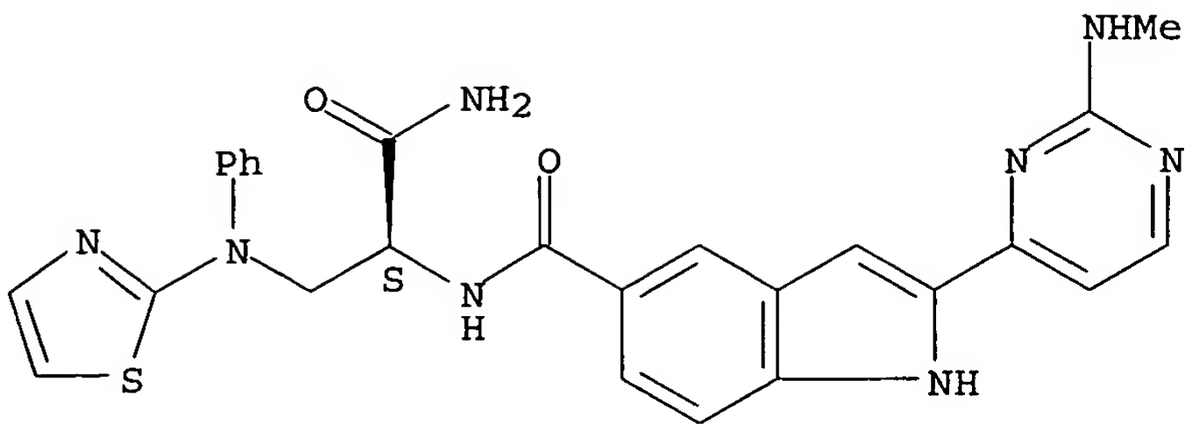


RN 673488-44-3 HCAPLUS
CN 1H-Indole-5-carboxamide, N-[2-[(4-fluorophenyl)-2-pyridinylamino]-1-(1H-1,2,4-triazol-3-yl)ethyl]-2-[2-(methylamino)-4-pyrimidinyl]- (9CI) (CA INDEX NAME)



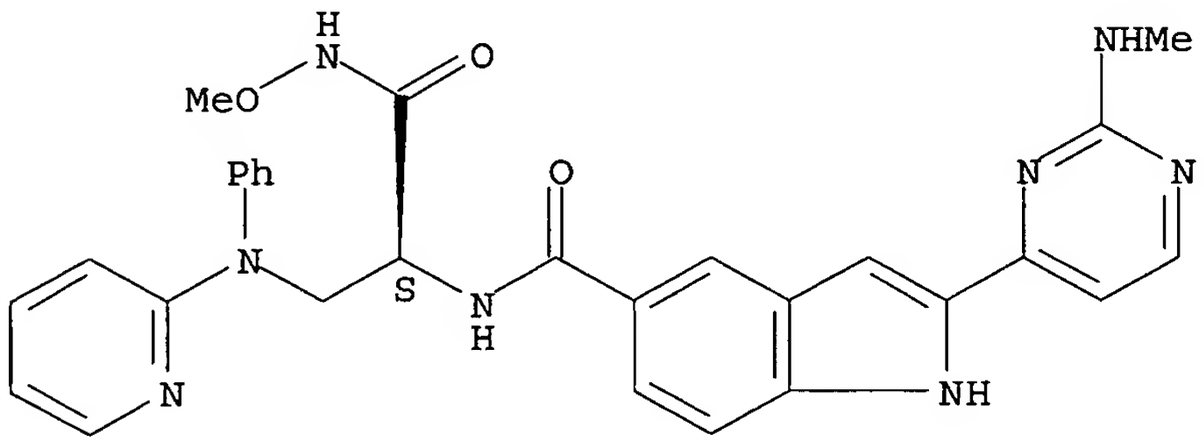
RN 673488-45-4 HCAPLUS
CN 1H-Indole-5-carboxamide, N-[(1S)-2-amino-2-oxo-1-[(phenyl-2-thiazolylamino)methyl]ethyl]-2-[2-(methylamino)-4-pyrimidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 673488-46-5 HCAPLUS
CN 1H-Indole-5-carboxamide, N-[(1S)-2-(methoxyamino)-2-oxo-1-[(phenyl-2-pyridinylamino)methyl]ethyl]-2-[2-(methylamino)-4-pyrimidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 673488-47-6 HCAPLUS
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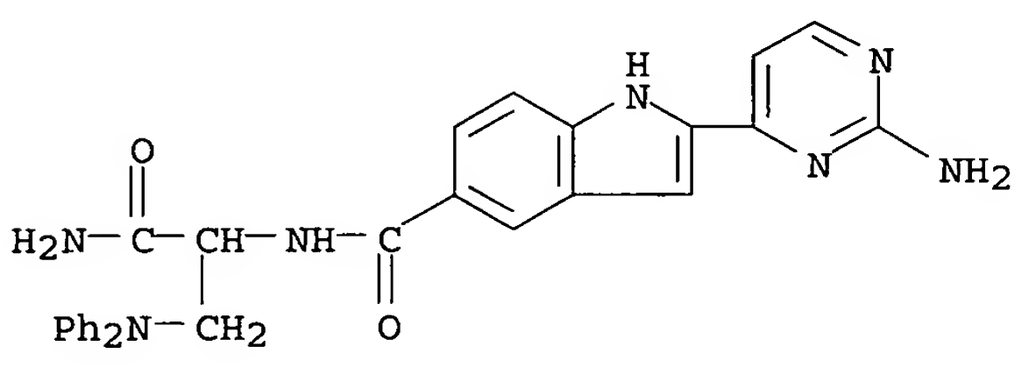
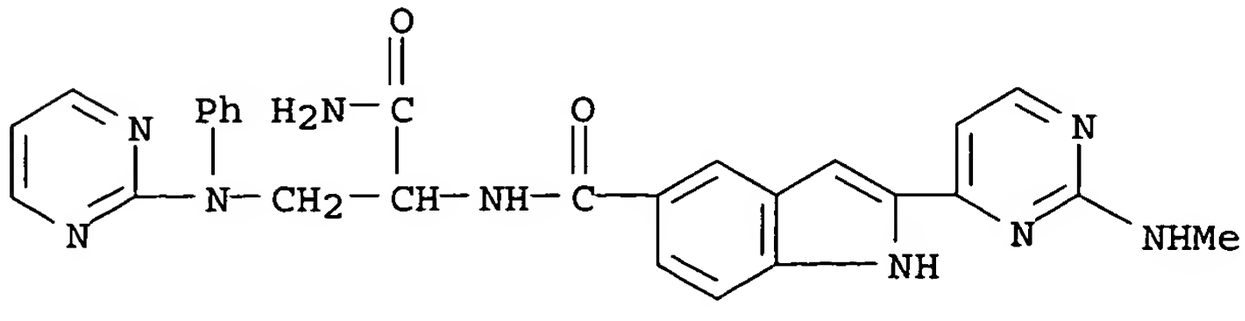
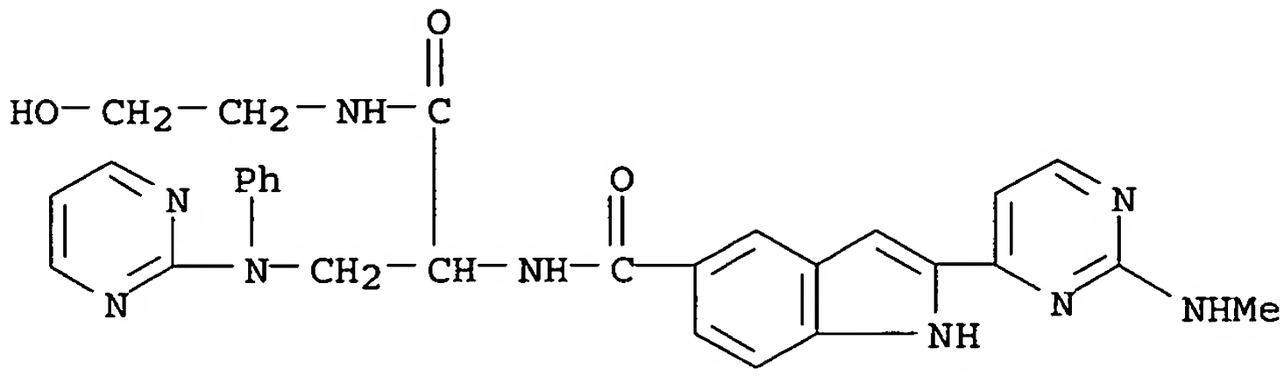


RN 673488-48-7 HCAPLUS
CN 1H-Indole-5-carboxamide, N-[2-amino-2-oxo-1-[(phenyl-2-pyrimidinylamino)methyl]ethyl]-2-[2-(methylamino)-4-pyrimidinyl]- (9CI) (CA INDEX NAME)



RN 673488-49-8 HCAPLUS
CN 1H-Indole-5-carboxamide, N-[2-[(2-hydroxyethyl)amino]-2-oxo-1-[(phenyl-2-pyrimidinylamino)methyl]ethyl]-2-[2-(methylamino)-4-pyrimidinyl]- (9CI) (CA INDEX NAME)



RN 673488-50-1 HCAPLUS
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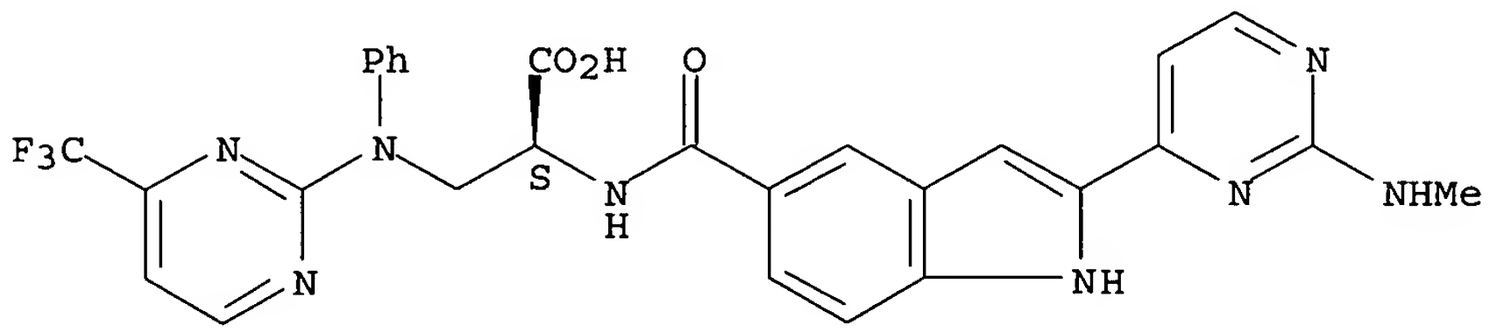
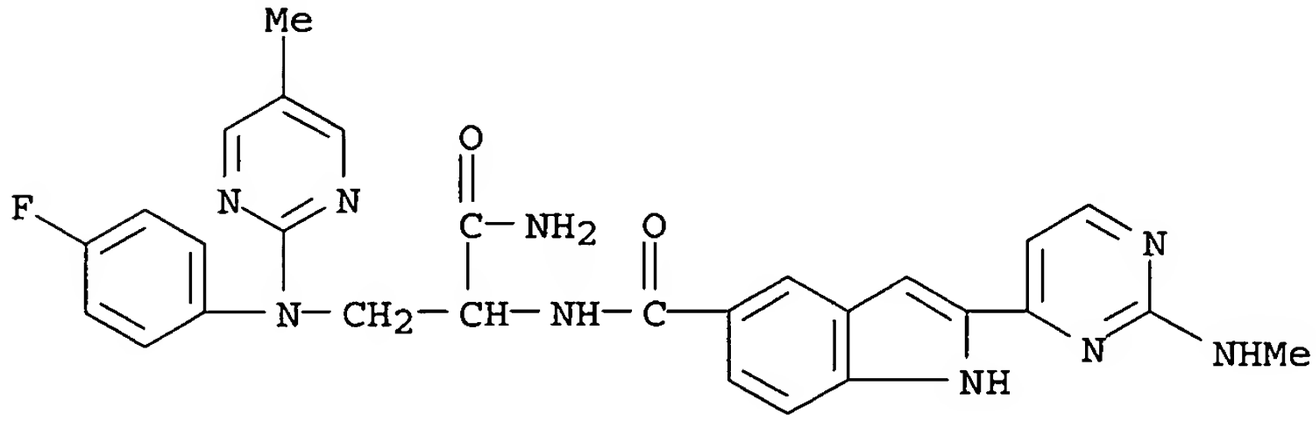
Absolute stereochemistry.



RN 673488-51-2 HCAPLUS
CN 1H-Indole-5-carboxamide, N-[2-amino-1-[[(4-fluorophenyl)(5-methyl-2-pyrimidinyl)amino]methyl]-2-oxoethyl]-2-[2-(methylamino)-4-pyrimidinyl]- (9CI) (CA INDEX NAME)



RN 673488-52-3 HCAPLUS
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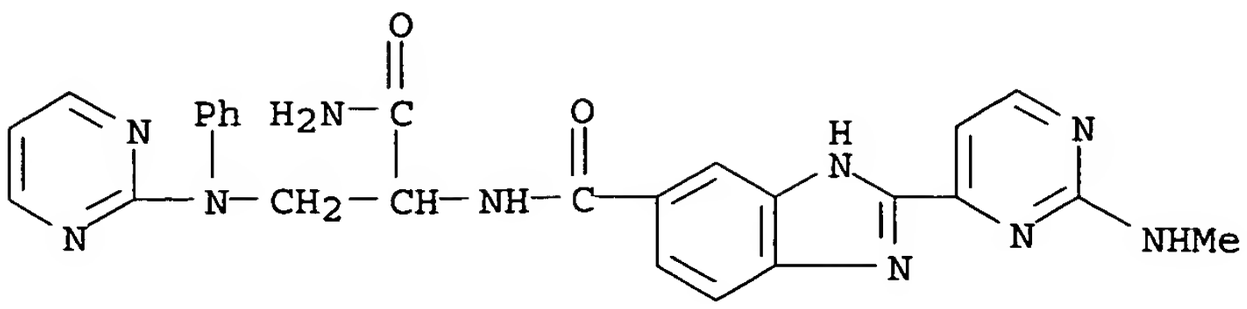
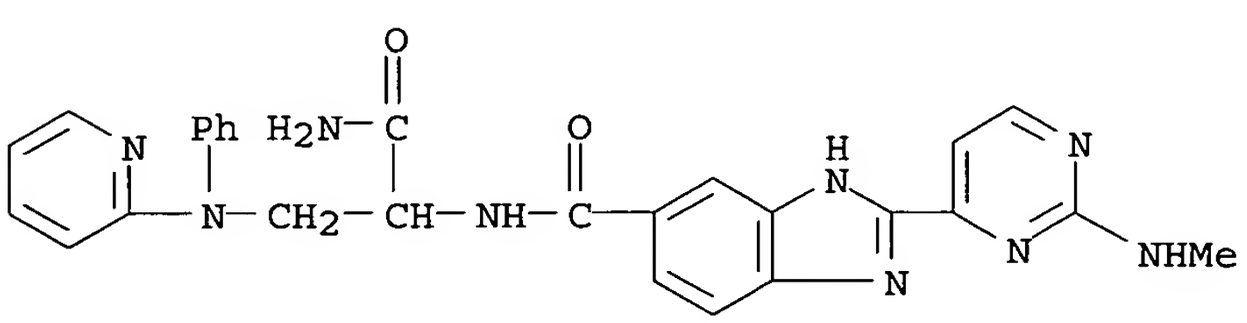
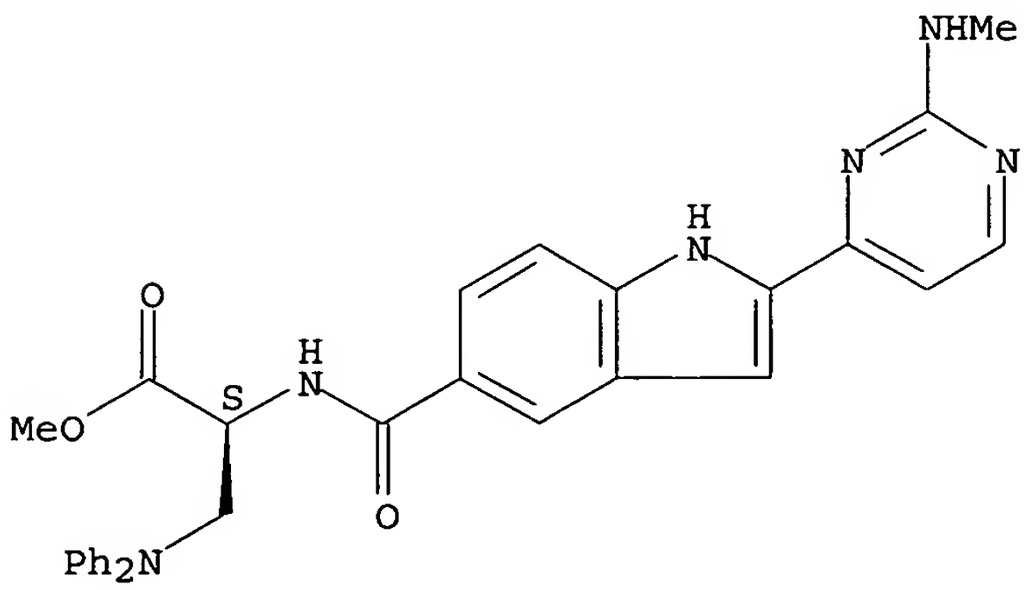


RN 673488-53-4 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[2-amino-2-oxo-1-[(phenyl-2-pyridinylamino)methyl]ethyl]-2-[2-(methylamino)-4-pyrimidinyl]- (9CI) (CA INDEX NAME)



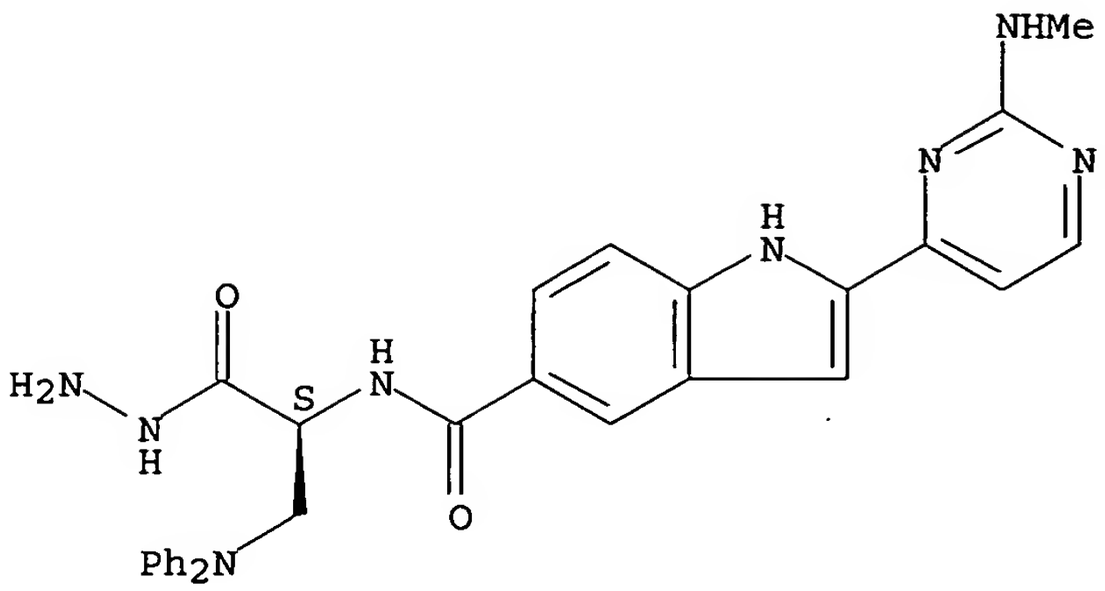
IT **669713-39-7P 669713-40-0P 669713-45-5P**
673488-56-7P 673488-58-9P 673488-59-0P
673488-61-4P 673488-62-5P 673488-63-6P
673488-64-7P 673488-67-0P 673488-71-6P
673488-72-7P 673488-73-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of pyrimidinylindolecarboxamides and pyrimidinylbenzimidazolecarboxamides as inhibitors of IκB kinase)
RN 669713-39-7 HCAPLUS
CN L-Alanine, 3-(diphenylamino)-N-[[2-[2-(methylamino)-4-pyrimidinyl]-1H-indol-5-yl]carbonyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



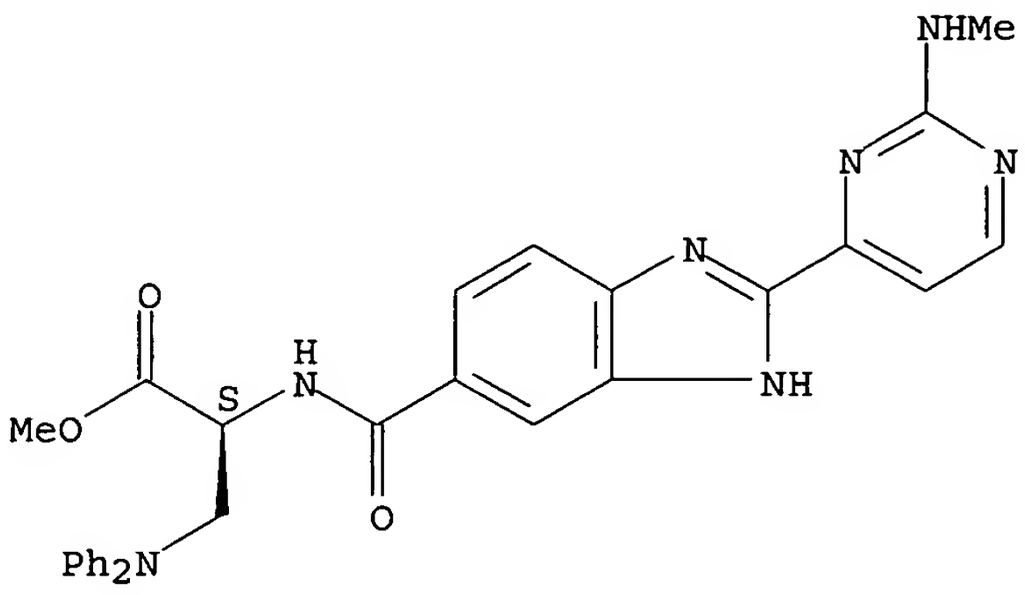
RN 669713-40-0 HCAPLUS
CN L-Alanine, 3-(diphenylamino)-N-[[2-[2-(methylamino)-4-pyrimidinyl]-1H-indol-5-yl]carbonyl]-, hydrazide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

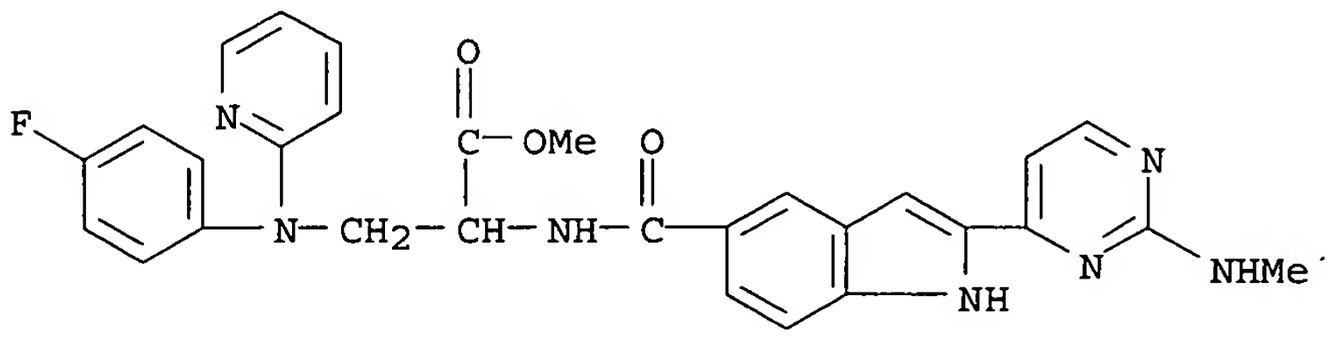


RN 669713-45-5 HCAPLUS
CN L-Alanine, 3-(diphenylamino)-N-[[2-[2-(methylamino)-4-pyrimidinyl]-1H-benzimidazol-5-yl]carbonyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

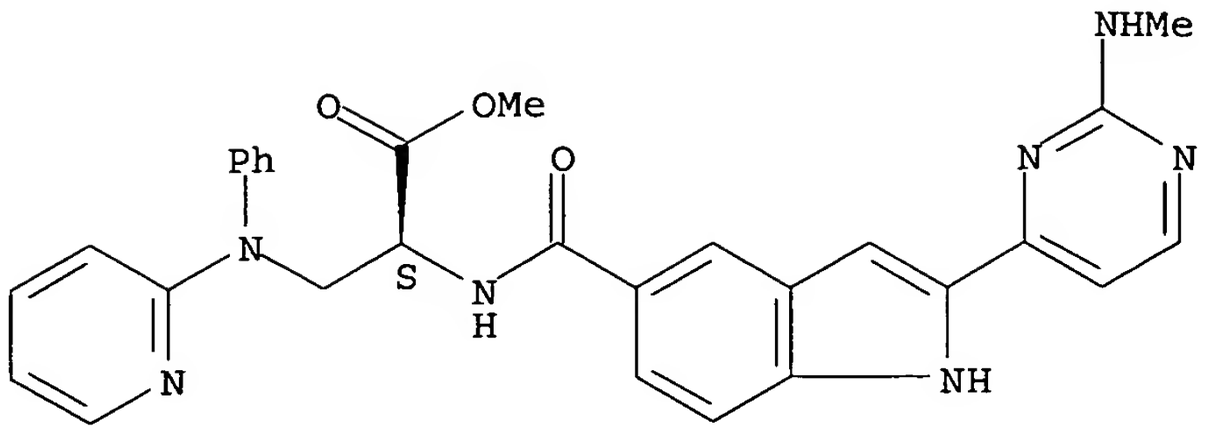


RN 673488-56-7 HCAPLUS
CN Alanine, 3-[(4-fluorophenyl)-2-pyridinylamino]-N-[[2-[2-(methylamino)-4-pyrimidinyl]-1H-indol-5-yl]carbonyl]-, methyl ester (9CI) (CA INDEX NAME)

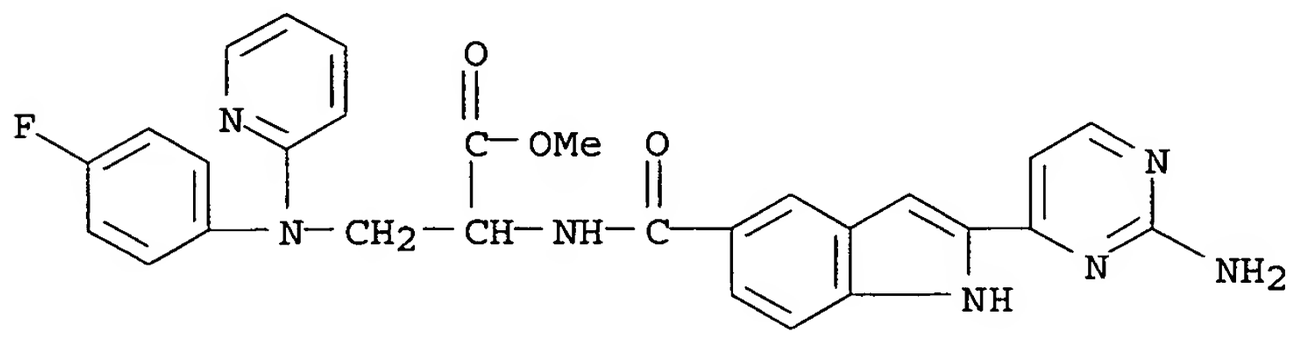


RN 673488-58-9 HCAPLUS
CN L-Alanine, N-[[2-[2-(methylamino)-4-pyrimidinyl]-1H-indol-5-yl]carbonyl]-3-(phenyl-2-pyridinylamino)-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

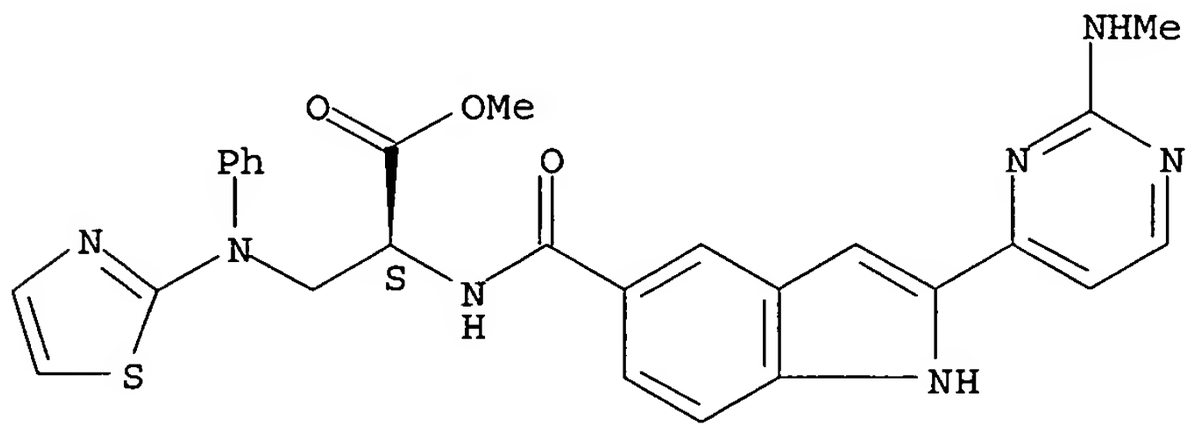


RN 673488-59-0 HCAPLUS
CN Alanine, N-[[2-(2-amino-4-pyrimidinyl)-1H-indol-5-yl]carbonyl]-3-[(4-fluorophenyl)-2-pyridinylamino]-, methyl ester (9CI) (CA INDEX NAME)

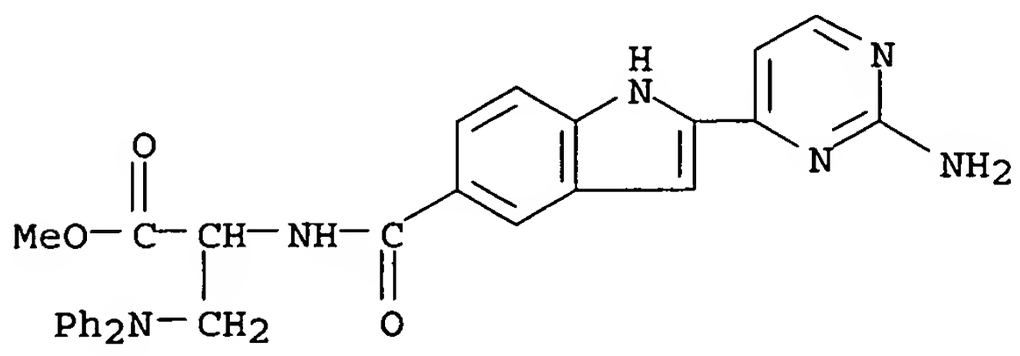


RN 673488-61-4 HCAPLUS
CN L-Alanine, N-[[2-[2-(methylamino)-4-pyrimidinyl]-1H-indol-5-yl]carbonyl]-3-(phenyl-2-thiazolylamino)-, methyl ester (9CI) (CA INDEX NAME)

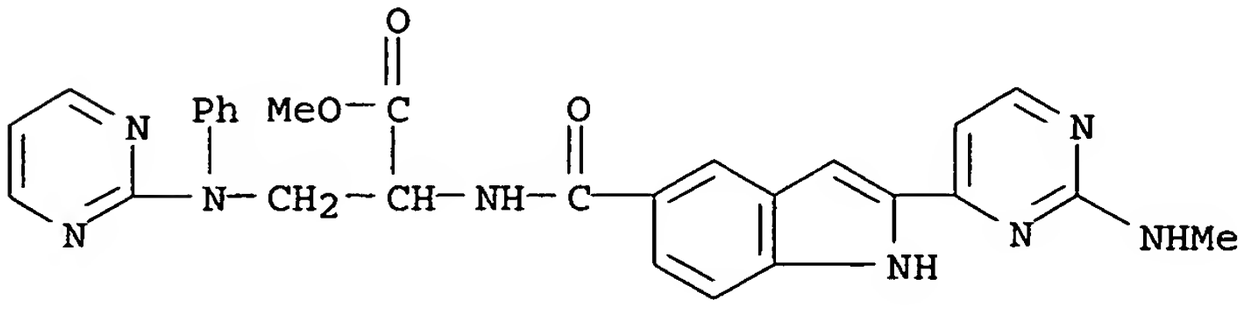
Absolute stereochemistry.



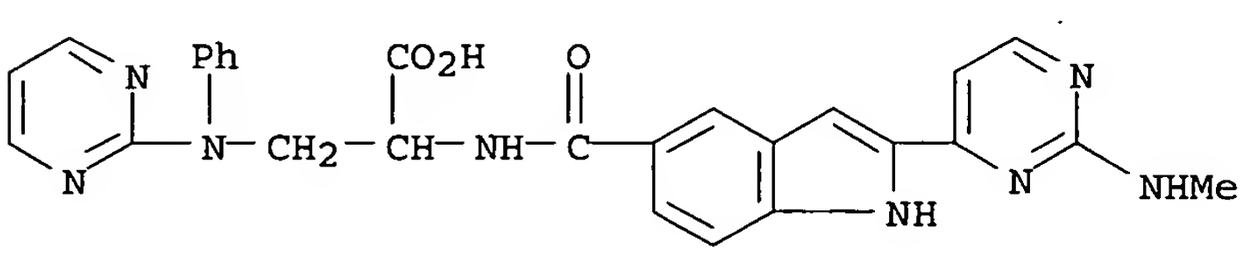
RN 673488-62-5 HCAPLUS
CN Alanine, N-[[2-(2-amino-4-pyrimidinyl)-1H-indol-5-yl]carbonyl]-3-(diphenylamino)-, methyl ester (9CI) (CA INDEX NAME)



RN 673488-63-6 HCAPLUS
CN Alanine, N-[[2-[2-(methylamino)-4-pyrimidinyl]-1H-indol-5-yl]carbonyl]-3-(phenyl-2-pyrimidinylamino)-, methyl ester (9CI) (CA INDEX NAME)

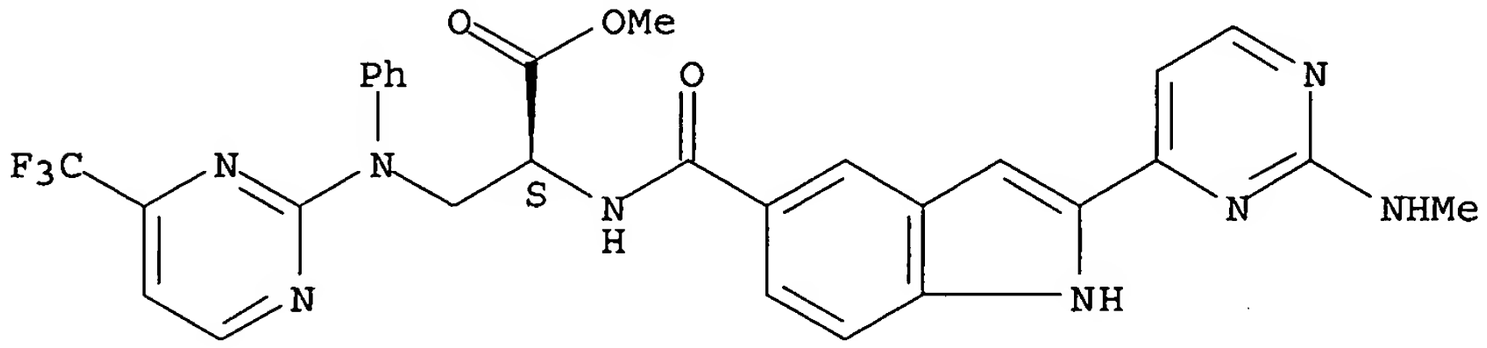


RN 673488-64-7 HCAPLUS
CN Alanine, N-[[2-[2-(methylamino)-4-pyrimidinyl]-1H-indol-5-yl]carbonyl]-3-(phenyl-2-pyrimidinylamino)- (9CI) (CA INDEX NAME)

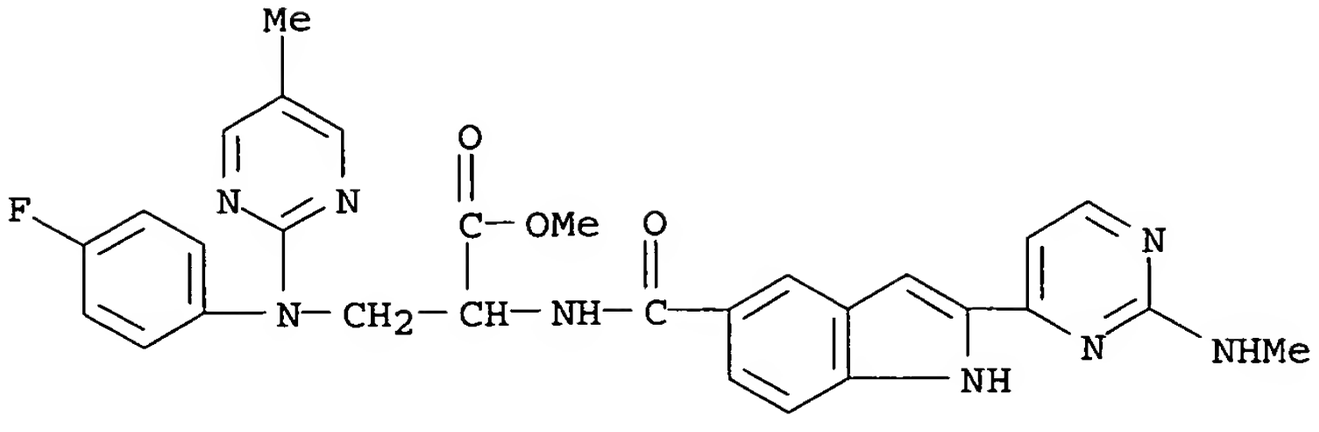


RN 673488-67-0 HCAPLUS
CN L-Alanine, N-[[2-[2-(methylamino)-4-pyrimidinyl]-1H-indol-5-yl]carbonyl]-3-[phenyl[4-(trifluoromethyl)-2-pyrimidinyl]amino]-, methyl ester (9CI) (CA INDEX NAME)

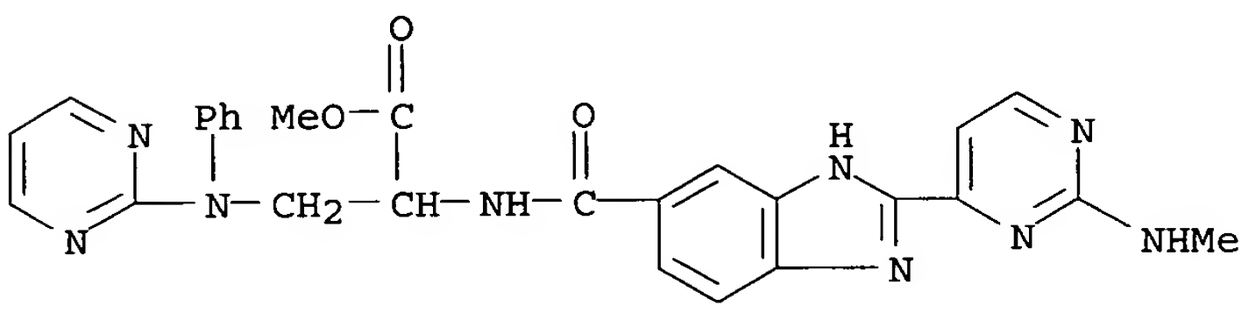
Absolute stereochemistry.



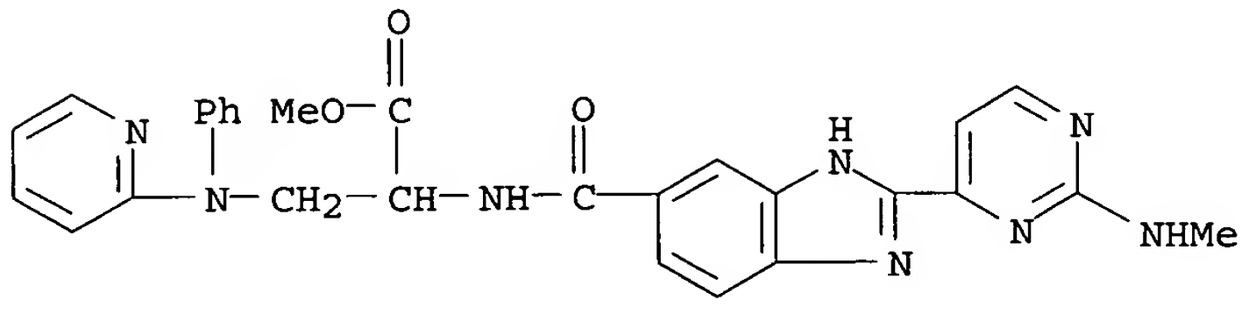
RN 673488-71-6 HCAPLUS
CN Alanine, 3-[(4-fluorophenyl)(5-methyl-2-pyrimidinyl)amino]-N-[[2-[2-(methylamino)-4-pyrimidinyl]-1H-indol-5-yl]carbonyl]-, methyl ester (9CI) (CA INDEX NAME)



RN 673488-72-7 HCAPLUS
CN Alanine, N-[[2-[2-(methylamino)-4-pyrimidinyl]-1H-benzimidazol-5-yl]carbonyl]-3-(phenyl-2-pyrimidinylamino)-, methyl ester (9CI) (CA INDEX NAME)



RN 673488-73-8 HCAPLUS
CN Alanine, N-[[2-[2-(methylamino)-4-pyrimidinyl]-1H-benzimidazol-5-yl]carbonyl]-3-(phenyl-2-pyridinylamino)-, methyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 3 OF 6 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:220204 HCAPLUS
DOCUMENT NUMBER: 140:247090
TITLE: Use of substituted indole and benzimidazole IκB kinase inhibitors for the treatment of **pain**
INVENTOR(S): Michaelis, Martin; Ritzeler, Olaf; Jaehne, Gerhard; Rudolphi, Karl; Geisslinger, Gerd; Schaible, Hans-Georg
PATENT ASSIGNEE(S): Aventis Pharma Deutschland GmbH, Germany
SOURCE: PCT Int. Appl., 75 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004022057	A1	20040318	WO 2003-EP8628	20030805
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10237723	A1	20040708	DE 2002-10237723	20020817
CA 2495455	AA	20040318	CA 2003-2495455	20030805
EP 1531819	A1	20050525	EP 2003-753349	20030805
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003013555	A	20050712	BR 2003-13555	20030805
US 2004116494	A1	20040617	US 2003-642974	20030818

PRIORITY APPLN. INFO.:	DE 2002-10237723	A	20020817
	US 2002-434628P	P	20021219
	WO 2003-EP8628	W	20030805

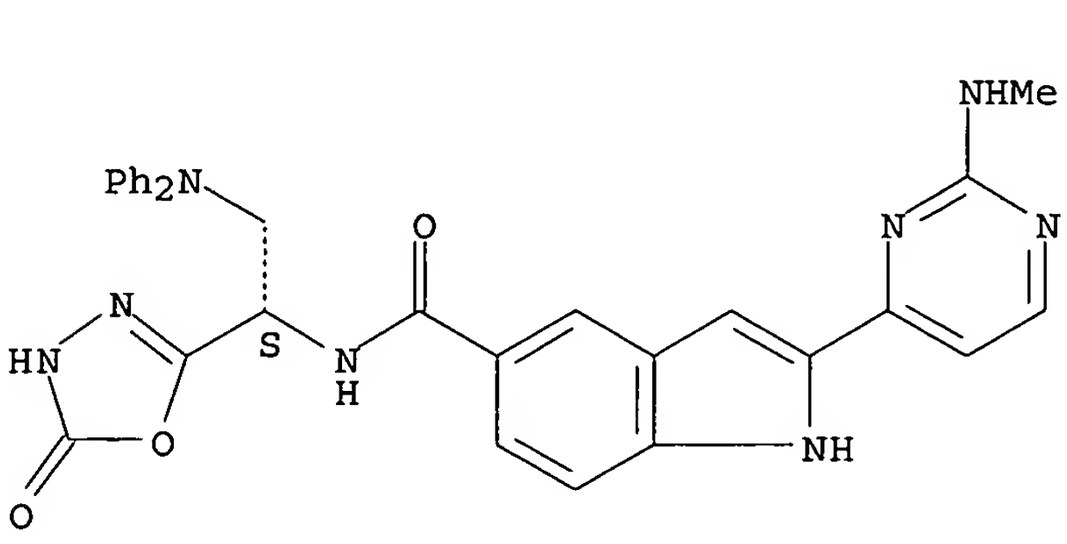
OTHER SOURCE(S): MARPAT 140:247090

AB The invention discloses the use of indole derivative and benzimidazole derivative
IκB kinase inhibitors that are suitable for producing medicaments for the treatment of **pain.** Preparation of compds. is described.

IT **669713-30-8P 669713-32-0P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(indole derivative and benzimidazole derivative IκB kinase inhibitors for the treatment of **pain**)

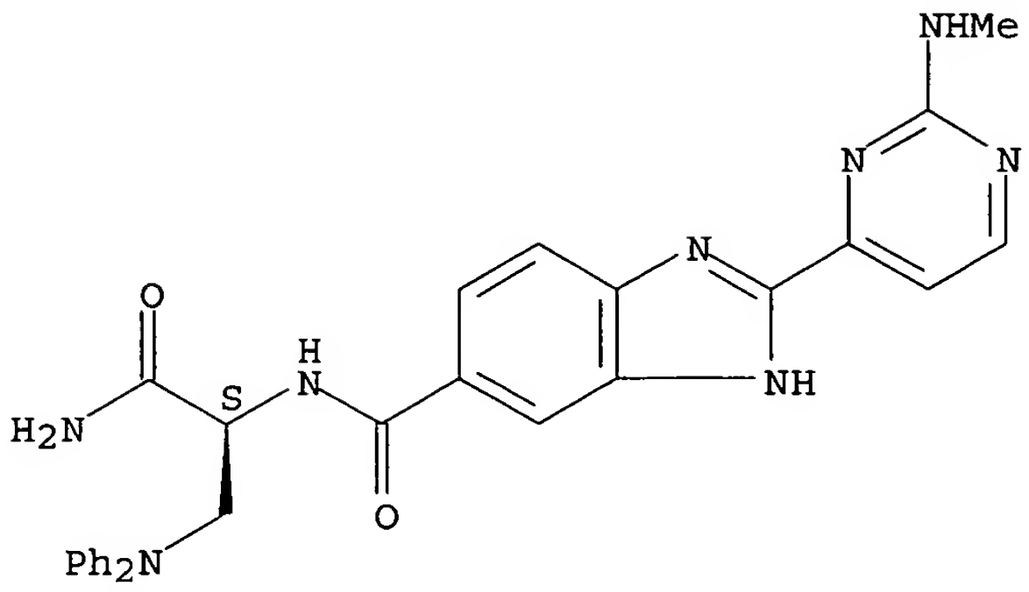
RN 669713-30-8 HCAPLUS
CN 1H-Indole-5-carboxamide, N-[(1S)-1-(4,5-dihydro-5-oxo-1,3,4-oxadiazol-2-yl)-2-(diphenylamino)ethyl]-2-[2-(methylamino)-4-pyrimidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 669713-32-0 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-2-amino-1-[(diphenylamino)methyl]-2-oxoethyl]-2-[2-(methylamino)-4-pyrimidinyl]- (9CI) (CA INDEX NAME)

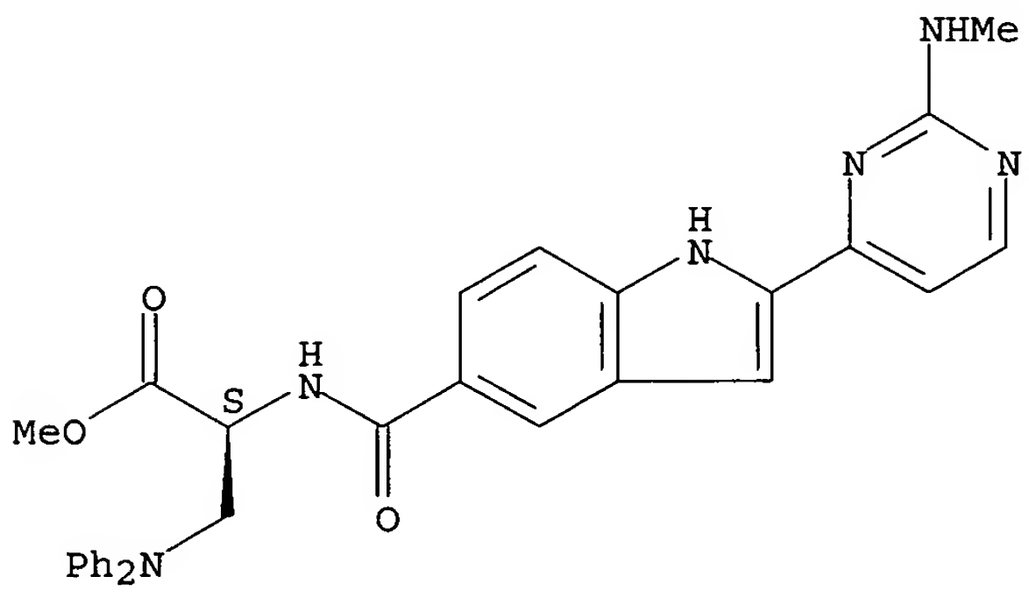
Absolute stereochemistry.



IT 669713-39-7P 669713-40-0P 669713-45-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(indole derivative and benzimidazole derivative IκB kinase inhibitors for the treatment of **pain**)

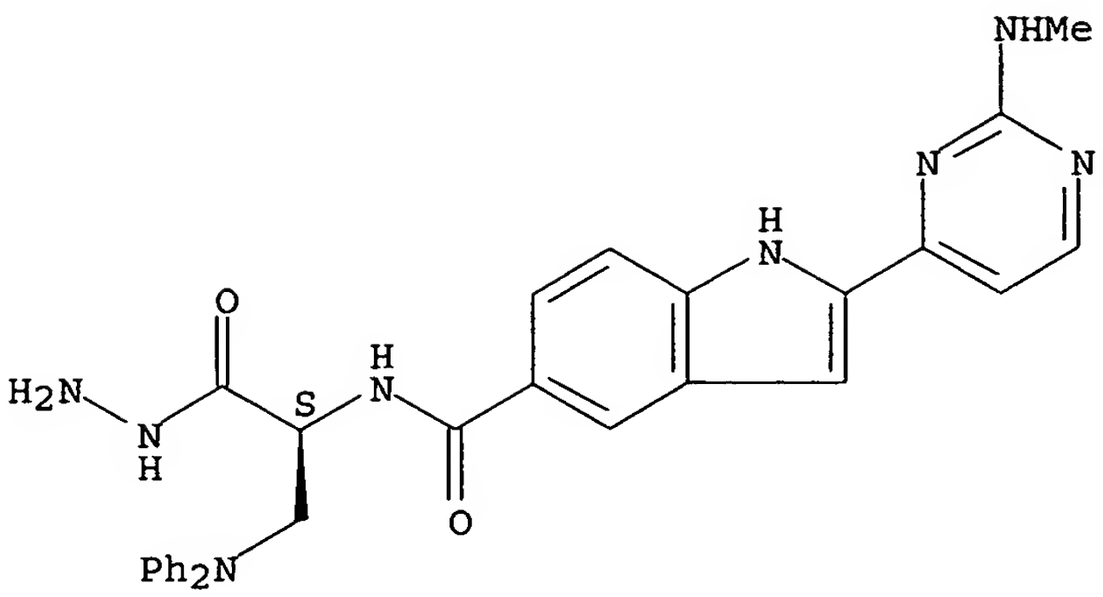
RN 669713-39-7 HCAPLUS
CN L-Alanine, 3-(diphenylamino)-N-[[2-[2-(methylamino)-4-pyrimidinyl]-1H-indol-5-yl]carbonyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



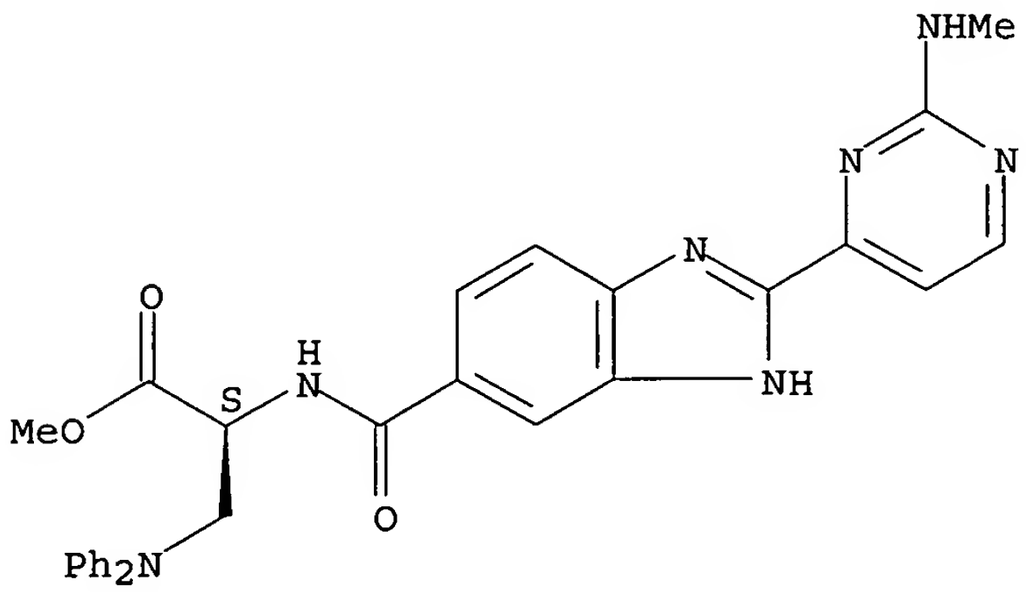
RN 669713-40-0 HCAPLUS
CN L-Alanine, 3-(diphenylamino)-N-[[2-[2-(methylamino)-4-pyrimidinyl]-1H-indol-5-yl]carbonyl]-, hydrazide (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 669713-45-5 HCAPLUS
CN L-Alanine, 3-(diphenylamino)-N-[[2-[2-(methylamino)-4-pyrimidinyl]-1H-benzimidazol-5-yl]carbonyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



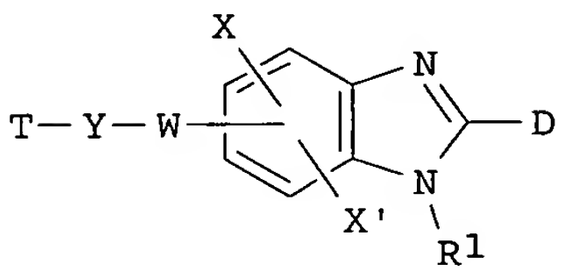
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 4 OF 6 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:177880 HCAPLUS
DOCUMENT NUMBER: 140:235708
TITLE: Preparation of benzimidazoles as coagulation factor Xa inhibitors for the treatment of thromboembolic illnesses
INVENTOR(S): Dorsch, Dieter; Cezanne, Bertram; Mederski, Werner; Tsaklakidis, Christos; Gleitz, Johannes; Barnes, Christopher
PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany
SOURCE: Ger. Offen., 34 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

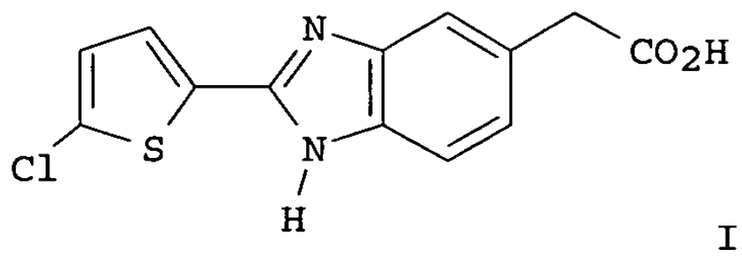
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10238002	A1	20040304	DE 2002-10238002	20020820

CA 2496139 AA 20040304 CA 2003-2496139 20030704
WO 2004017963 A1 20040304 WO 2003-EP7180 20030704
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
BR 2003013634 A 20050621 BR 2003-13634 20030704
EP 1558247 A1 20050803 EP 2003-792176 20030704
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
PRIORITY APPLN. INFO.: DE 2002-10238002 A 20020820
WO 2003-EP7180 W 20030704
OTHER SOURCE(S): MARPAT 140:235708

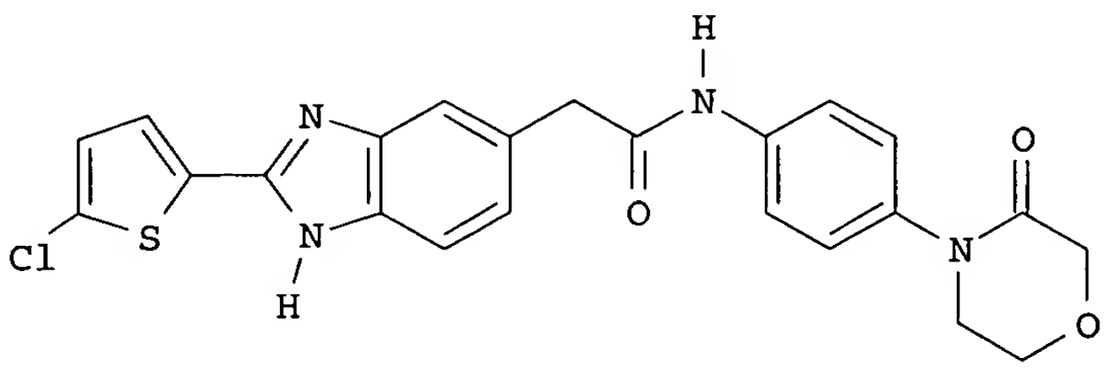
GI



I



II



III

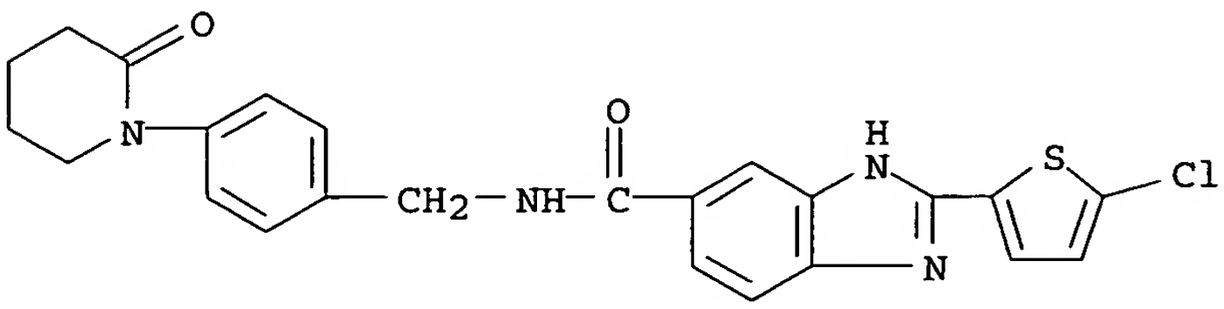
AB Title compds. I [D = halo, A, OR2, etc.; X, X' = N, halo, A, etc.; R1 = H, A; R2 = H, A, [C(R1)]n-Ar', etc.; Y = alkylene, cycloalkylene, Het-diyl (sic), etc.; T = aromatic, heterocyclic; W = [C(R2)2]nCONR2[C(R2)2]n, [C(R2)2]nNR2CO[C(R2)2]n, [C(R2)2]nO[C(R2)2]n, etc.; A = (un)substituted alkyl with provisos; Ar' = (un)substituted Ph e.g., halo, A, OR1, etc.; n = 0-2] and their pharmaceutically acceptable salts and formulations were prepared For example, coupling of acid II, e.g., prepared from 2-chlorothiophen-5-aldehyde in 2-steps, and 4-(4-aminophenyl)morpholin-3-one afforded benzimidazole III. In coagulation factor Xa inhibition assays, 3-examples of compds. I exhibited IC50 values ranging from 1.2-2.3 x 10-7 M, e.g., the IC50 value of benzimidazole III was 2.3 x 10-7 M. Compds. I are claimed useful for the treatment of thromboembolic illnesses and tumors.

IT **666817-33-0P**, 1-[2-(5-Chlorothiophen-2-yl)-1H-benzimidazol-5-yl]-N-[4-(2-oxopiperidin-1-yl)benzyl]formamide
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES

(Uses)
(preparation of benzimidazoles as coagulation factor Xa inhibitors for the treatment of thromboembolic illnesses)

RN 666817-33-0 HCAPLUS

CN 1H-Benzimidazole-5-carboxamide, 2-(5-chloro-2-thienyl)-N-[[4-(2-oxo-1-piperidinyl)phenyl]methyl]- (9CI) (CA INDEX NAME)



L7 ANSWER 5 OF 6 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:644460 HCAPLUS

DOCUMENT NUMBER: 139:173825

TITLE: Neurotrophin-inhibiting condensed pyrazoles and analgesics containing them

INVENTOR(S): Tanaka, Masahiro; Yuno, Takeo; Kitagawa, Yoshihiro

PATENT ASSIGNEE(S): Japan Tobacco, Inc., Japan

SOURCE: Jpn. Kokai Tokkyo Koho, 39 pp.
CODEN: JKXXAF

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

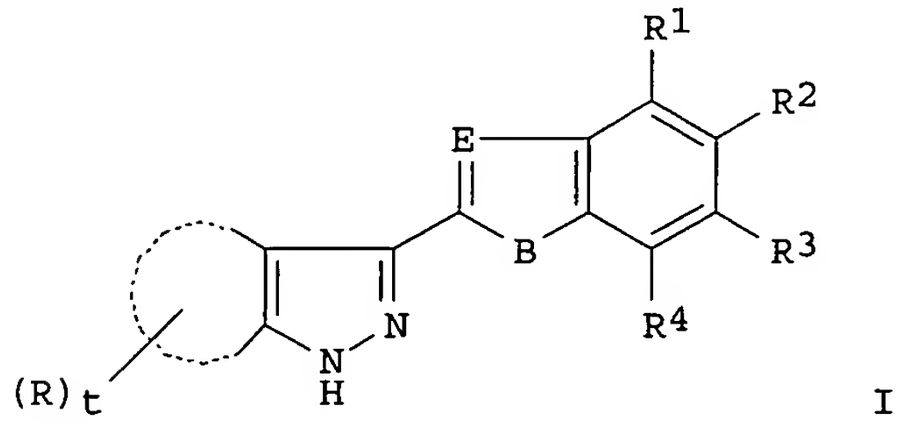
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2003231687	A2	20030819	JP 2002-27454	20020204

PRIORITY APPLN. INFO.: JP 2002-27454 20020204

OTHER SOURCE(S): MARPAT 139:173825

GI



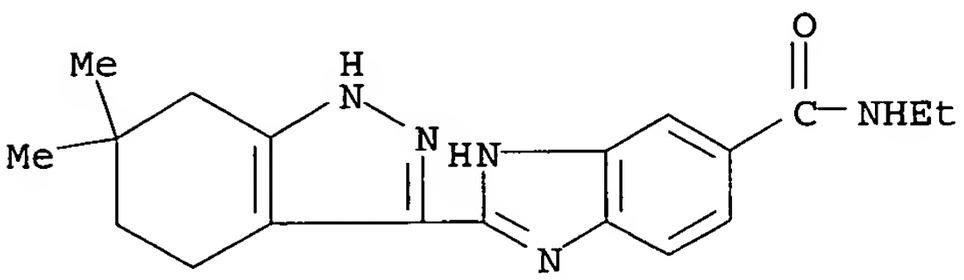
I

AB Analgesics contain condensed pyrazolyl compds. I (R1-R4 = XYX'Y'X''Z; Z = H, halo, NO2, cyano, etc.; X, X', X'' = single bond, C1-6 alkylene, vinylene, ethynylene, etc.; Y, Y' = single bond, O, O2C, CO, CO2, etc.; ring A = 5- to 7-membered ring containing C, N, and O or its spiro derivative; R =
C1-6 alkyl, C6-10 carbocyclyl, OH, C1-6 alkoxy, etc.; t = 1-3; E = N, CR5; if E = N, then B = NR5, O, S, CH:CH; if E = CR5, then B = NR5; R5 = H,

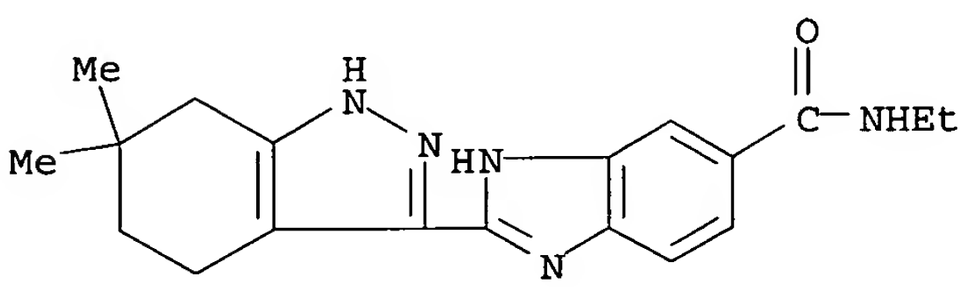
C1-6 alkyl) or their salts. Me 4-amino-3-(6,6-dimethyl-4,5,6,7-tetrahydroindazol-3-ylcarbonylamino)benzoate (preparation given) was heated with AcOH at 120° for 3 h to give 96% I (R1 = R3 = R4 = H, R2 = CO2Me, E = N, B = NH, ring A = 4,4-dimethylcyclohexene), which in vitro inhibited TrkA with IC50 of 0.19 μM.

IT **581082-12-4P 581082-13-5P 581082-63-5P**
581082-66-8P 581082-67-9P 581082-68-0P
581082-69-1P 581082-72-6P 581082-73-7P
581082-77-1P 581082-78-2P 581082-79-3P
581082-80-6P 581082-81-7P 581082-89-5P
581083-09-2P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of neurotrophin-inhibiting condensed pyrazoles as analgesics)

RN 581082-12-4 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-ethyl-2-(4,5,6,7-tetrahydro-6,6-dimethyl-1H-indazol-3-yl)- (9CI) (CA INDEX NAME)

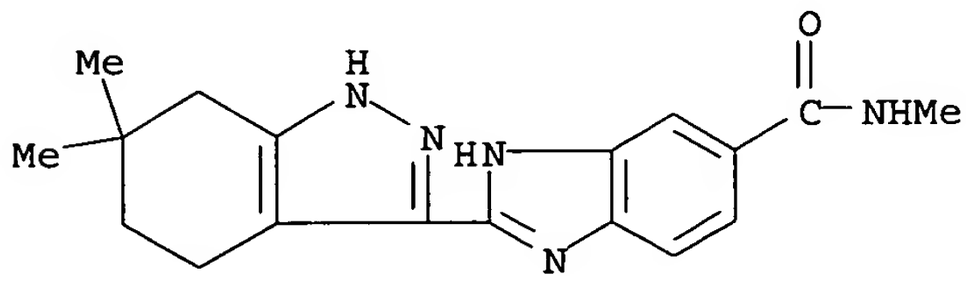


RN 581082-13-5 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-ethyl-2-(4,5,6,7-tetrahydro-6,6-dimethyl-1H-indazol-3-yl)-, monohydrochloride (9CI) (CA INDEX NAME)



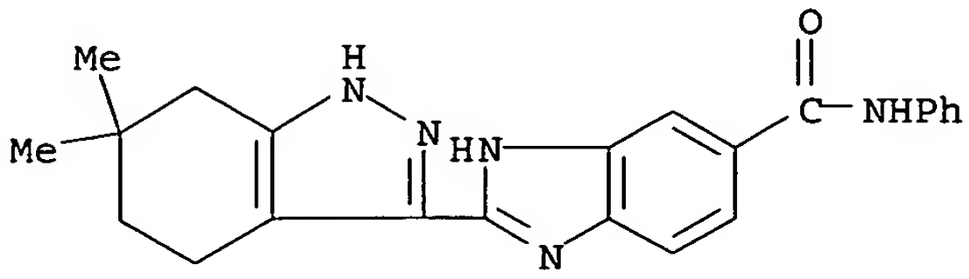
● HCl

RN 581082-63-5 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-methyl-2-(4,5,6,7-tetrahydro-6,6-dimethyl-1H-indazol-3-yl)- (9CI) (CA INDEX NAME)

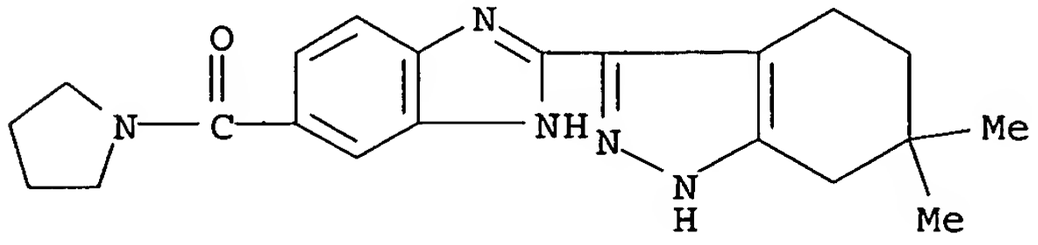


RN 581082-66-8 HCAPLUS

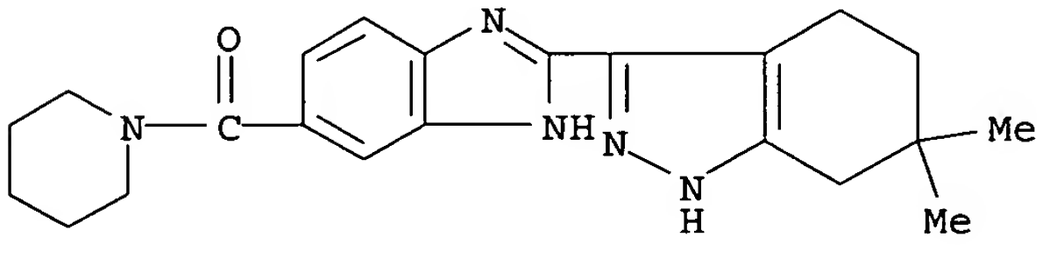
CN 1H-Benzimidazole-5-carboxamide, N-phenyl-2-(4,5,6,7-tetrahydro-6,6-dimethyl-1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



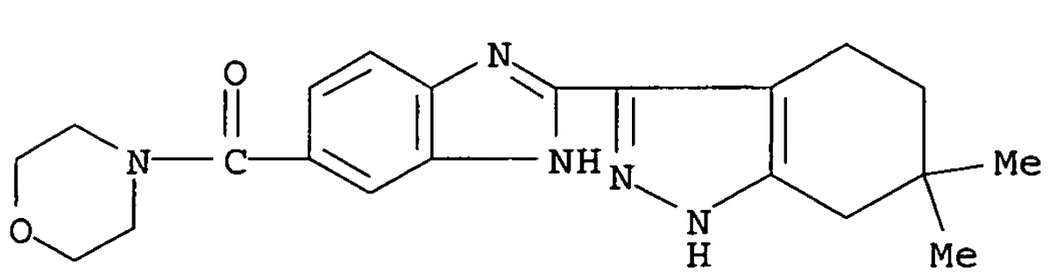
RN 581082-67-9 HCAPLUS
CN Pyrrolidine, 1-[[2-(4,5,6,7-tetrahydro-6,6-dimethyl-1H-indazol-3-yl)-1H-benzimidazol-5-yl]carbonyl]- (9CI) (CA INDEX NAME)



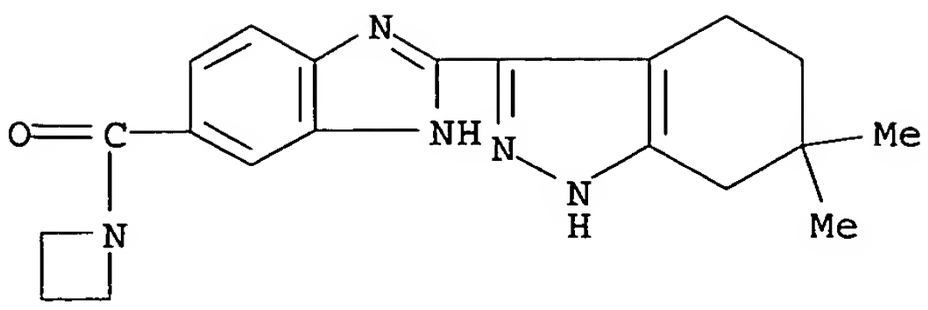
RN 581082-68-0 HCAPLUS
CN Piperidine, 1-[[2-(4,5,6,7-tetrahydro-6,6-dimethyl-1H-indazol-3-yl)-1H-benzimidazol-5-yl]carbonyl]- (9CI) (CA INDEX NAME)



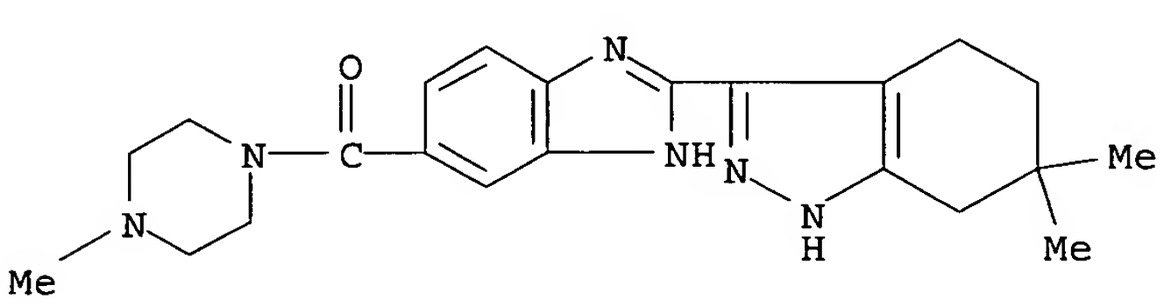
RN 581082-69-1 HCAPLUS
CN Morpholine, 4-[[2-(4,5,6,7-tetrahydro-6,6-dimethyl-1H-indazol-3-yl)-1H-benzimidazol-5-yl]carbonyl]- (9CI) (CA INDEX NAME)



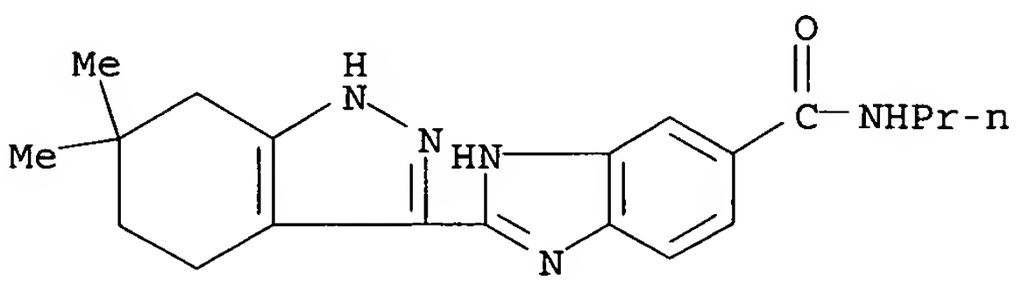
RN 581082-72-6 HCAPLUS
CN Azetidine, 1-[[2-(4,5,6,7-tetrahydro-6,6-dimethyl-1H-indazol-3-yl)-1H-benzimidazol-5-yl]carbonyl]- (9CI) (CA INDEX NAME)



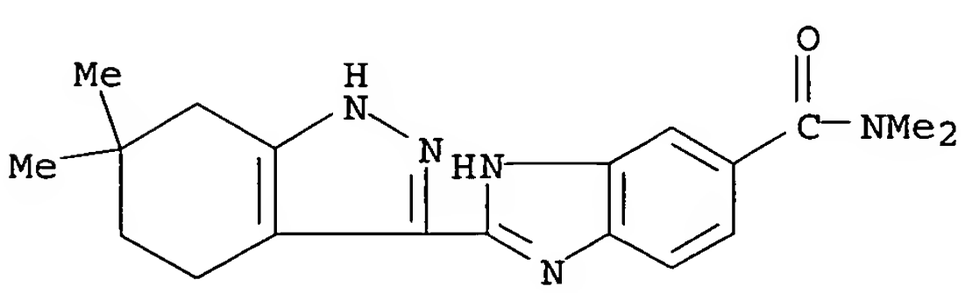
RN 581082-73-7 HCAPLUS
CN Piperazine, 1-methyl-4-[[2-(4,5,6,7-tetrahydro-6,6-dimethyl-1H-indazol-3-yl)-1H-benzimidazol-5-yl]carbonyl]- (9CI) (CA INDEX NAME)



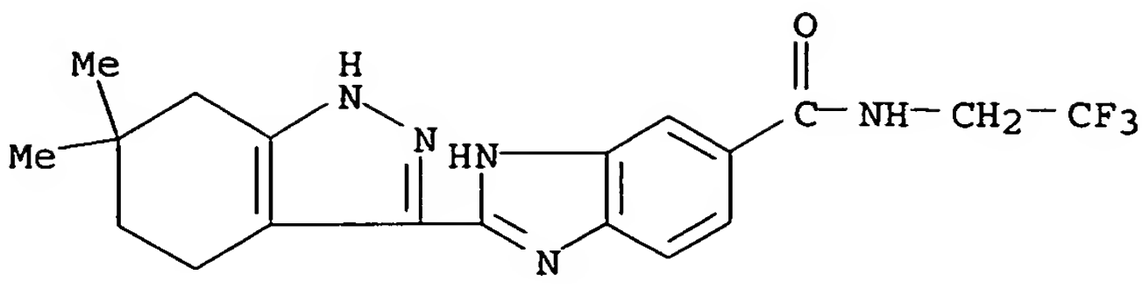
RN 581082-77-1 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-propyl-2-(4,5,6,7-tetrahydro-6,6-dimethyl-1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



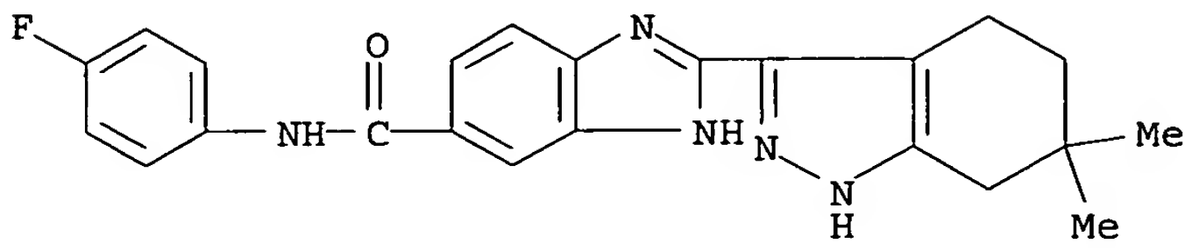
RN 581082-78-2 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N,N-dimethyl-2-(4,5,6,7-tetrahydro-6,6-dimethyl-1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



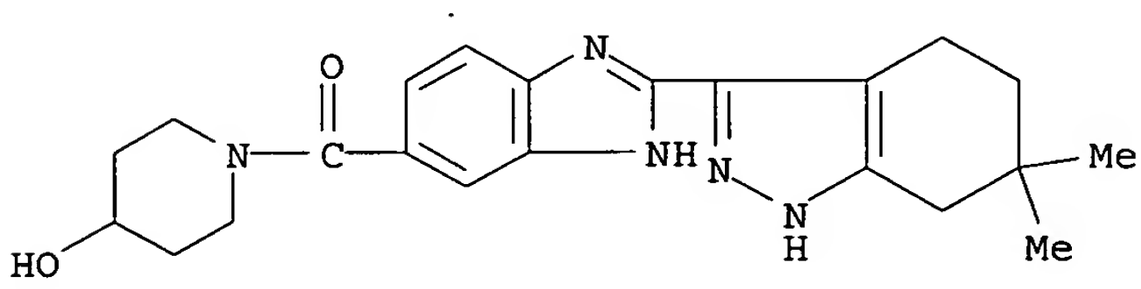
RN 581082-79-3 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, 2-(4,5,6,7-tetrahydro-6,6-dimethyl-1H-indazol-3-yl)-N-(2,2,2-trifluoroethyl)- (9CI) (CA INDEX NAME)



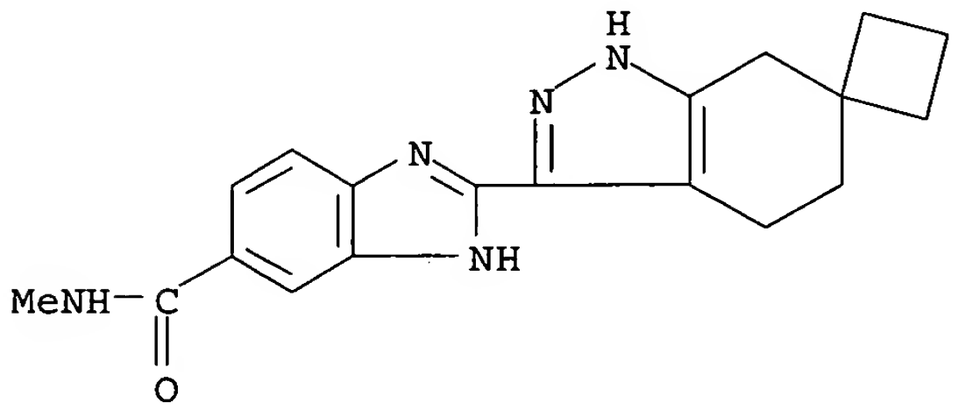
RN 581082-80-6 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-(4-fluorophenyl)-2-(4,5,6,7-tetrahydro-6,6-dimethyl-1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



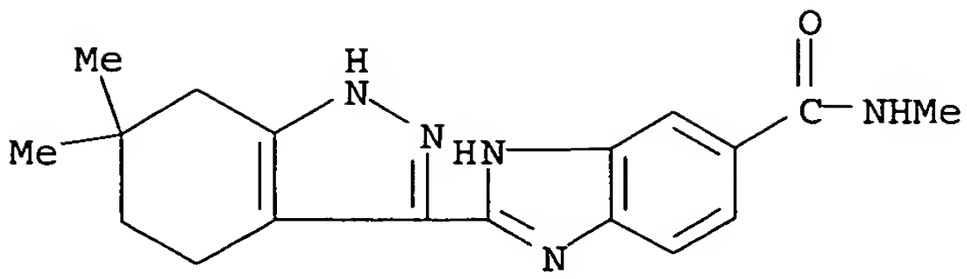
RN 581082-81-7 HCAPLUS
CN 4-Piperidinol, 1-[[2-(4,5,6,7-tetrahydro-6,6-dimethyl-1H-indazol-3-yl)-1H-benzimidazol-5-yl]carbonyl]- (9CI) (CA INDEX NAME)



RN 581082-89-5 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-methyl-2-(1',4',5',7'-tetrahydrospiro[cyclobutane-1,6'-[6H]indazol]-3'-yl)- (9CI) (CA INDEX NAME)



RN 581083-09-2 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-methyl-2-(4,5,6,7-tetrahydro-6,6-dimethyl-1H-indazol-3-yl)-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

L7 ANSWER 6 OF 6 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:334903 HCAPLUS
DOCUMENT NUMBER: 138:353988
TITLE: Preparation of benzimidazoles and analogs and their use as protein kinase inhibitors
INVENTOR(S): Edwards, Michael Louis; Cox, Paul Joseph; Amendola, Shelley; Deprets, Stephanie Daniele; Gillespy, Timothy Alan; Edlin, Christopher David; Morley, Andrew David; Gardner, Charles J.; Pedgrift, Brian; Bouchard, Herve; Babin, Didier; Gauzy, Laurence; Le Brun, Alain; Majid, Tahir Nedeem; Reader, John C.; Payne, Lloyd J.; Khan, Nawaz M.; Cherry, Michael
PATENT ASSIGNEE(S): Aventis Pharmaceuticals Inc., USA
SOURCE: PCT Int. Appl., 711 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003035065	A1	20030501	WO 2002-GB4763	20021024
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
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FR 2831537	A1	20030502	FR 2001-13868	20011026
CA 2465247	AA	20030501	CA 2002-2465247	20021024
US 2004048868	A1	20040311	US 2002-279834	20021024
US 6897208	B2	20050524		
EP 1441725	A1	20040804	EP 2002-801954	20021024
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
BR 2002013562	A	20040831	BR 2002-13562	20021024
JP 2005509633	T2	20050414	JP 2003-537632	20021024

PRIORITY APPLN. INFO.:
FR 2001-13868 A 20011026
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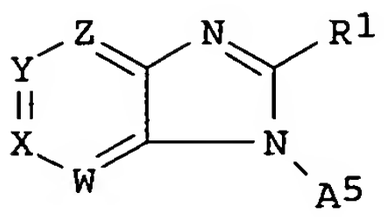
GB 2002-6895 A 20020322

US 2002-395060P P 20020711
US 2002-395151P P 20020711
WO 2002-GB4763 W 20021024

OTHER SOURCE(S): MARPAT 138:353988

GI



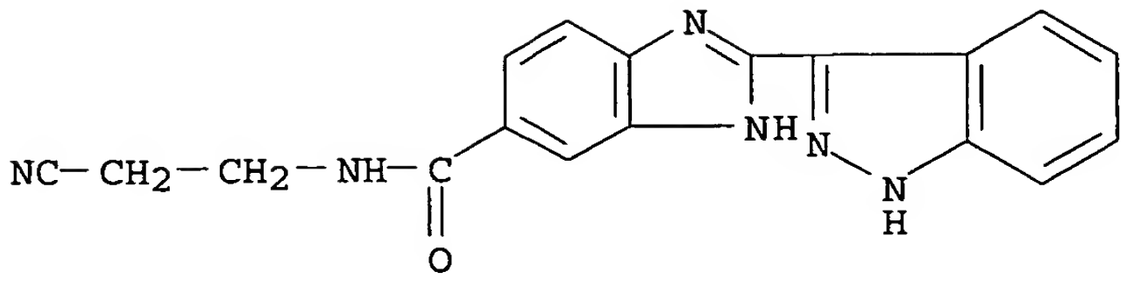
I

AB The invention is directed to physiol. active benzimidazoles and analogs (shown as I; variables defined below; e.g. 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid benzylamide) and compns. containing such compds., and their prodrugs, and pharmaceutically acceptable salts and solvates of such compds. and their prodrugs, as well as to novel I and to processes for their preparation Such compds. and compns. have valuable pharmaceutical properties, in particular the ability to inhibit kinases. For I: X = C-R2 and W, Y and Z = CH or CR3; or W = CH, X = N, Y = CH or CR3, and Z = CH or CR3; or W = N, X = CH or CR2, Y = CH and CR3, and Z = CH or CR3; or W = N, X = CH or CR2, Y = N, and Z is CH or CR3; or W = N, X = CH or CR2, Y = CH or CR3, and Z = N; or W = N, X = N, Y = CH or CR3, and Z = CH or CR3. A5 = H or alkyl; R1 = optionally substituted aryl or heteroaryl; addnl. details are given in the claims. IC50 values for >200 I are tabulated for inhibition of KDR receptor tyrosine kinase. Particular I inhibit SYK activity with IC50's = 100 μM to 0.1 nM. Particular I inhibit ITK activity with IC50's = 100 μM to 1 μM. I inhibit the increase in edema observed in a sensitized mouse ear following antigen exposure and inhibit mast cell activation and functional responses when given orally in a mouse model of passive cutaneous anaphylaxis. Methods of preparation are claimed and hundreds of example prepns. of I and intermediates leading to them are included. For example, 20 mg 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid benzylamide was prepared from 20 mg 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid and benzylamine in DMF in the presence of HBTU followed by addition of N,N-diisopropylethylamine; the acid was prepared in several steps starting from 3-indazolecarboxylic acid and involving intermediates Me 3-indazolecarboxylate, (1H-indazol-3-yl)methanol and 1H-indazole-3-carboxaldehyde.

IT **518988-18-6P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (2-cyanoethyl)amide
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(drug candidate; preparation of benzimidazoles and analogs and their use as protein kinase inhibitors)

RN 518988-18-6 HCAPLUS

CN 1H-Benzimidazole-5-carboxamide, N-(2-cyanoethyl)-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



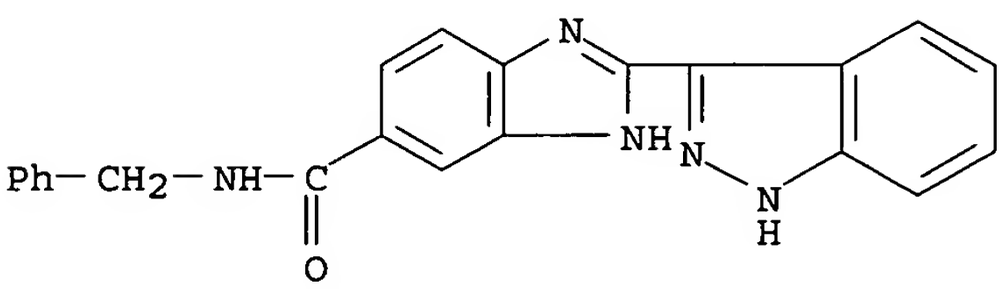
IT **518355-10-7P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid benzylamide **518355-11-8P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-methylamide **518355-12-9P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-ethylamide **518355-13-0P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-isopropylamide **518355-14-1P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-phenylamide **518355-15-2P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-phenethylamide **518355-16-3P**, [2-(1H-Indazol-3-yl)-1H-benzimidazol-5-yl]morpholinomethanone **518355-17-4P**, [2-(1H-Indazol-3-yl)-1H-benzimidazol-5-yl](4-methylpiperazin-1-yl)methanone **518355-18-5P** **518355-19-6P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-(isobutyl)amide **518355-20-9P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-(cyclohexylmethyl)amide **518355-22-1P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-(2-furfuryl)amide **518355-23-2P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-benzyl-N-methylamide **518355-36-7P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-sulfamoylbenzylamide **518355-37-8P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (3-ethoxypropyl)amide **518355-38-9P** , 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-bromobenzylamide **518355-39-0P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-methanesulfonylbenzylamide **518355-40-3P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (naphthalen-1-ylmethyl)amide **518355-41-4P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-trifluoromethylbenzylamide **518355-42-5P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (thiophen-2-ylmethyl)amide **518355-43-6P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-dimethylaminobenzylamide **518355-44-7P**, 4-[[[2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carbonyl]amino]methyl]piperidine-1-carboxylic acid tert-butyl ester **518355-45-8P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-nitrobenzylamide **518355-46-9P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (pyridin-3-ylmethyl)amide **518355-47-0P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 3-bromobenzylamide **518355-48-1P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 3-methoxybenzylamide **518355-49-2P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide **518355-50-5P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (benzo[b]thiophen-3-ylmethyl)amide **518355-51-6P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (1,3-dimethyl-1H-pyrazol-4-ylmethyl)amide **518355-52-7P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 2-trifluoromethoxybenzylamide **518355-53-8P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 2-methylbenzylamide **518355-54-9P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (3-methylthiophen-2-ylmethyl)amide **518355-56-1P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 2-trifluoromethylbenzylamide **518355-57-2P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-phenoxybenzylamide

518355-58-3P, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 3-trifluoromethoxybenzylamide **518355-59-4P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (3-isopropoxypropyl)amide **518355-60-7P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (1-methyl-1H-pyrazol-4-ylmethyl)amide **518355-61-8P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-isopropylbenzylamide **518355-62-9P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (2,5-dimethylfuran-3-ylmethyl)amide **518355-63-0P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (benzo[b]thiophen-2-ylmethyl)amide **518355-64-1P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid [3-(3-acetylaminophenoxy)propyl]amide **518355-65-2P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (6-chloropyridin-3-ylmethyl)amide **518355-66-3P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid ([2,2']bithiophenyl-5-ylmethyl)amide **518355-67-4P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (2,3-dihydrobenzofuran-5-ylmethyl)amide **518355-68-5P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-cyanobenzylamide **518355-69-6P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (5-chlorobenzo[b]thiophen-3-ylmethyl)amide **518355-70-9P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 3-trifluoromethylbenzylamide **518355-71-0P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 2-methylsulfanylbenzylamide **518355-72-1P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (tetrahydropyran-4-ylmethyl)amide **518355-73-2P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (2,3-dihydrobenzo[1,4]dioxin-2-ylmethyl)amide **518355-74-3P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (furan-3-ylmethyl)amide **518355-75-4P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 2-nitrobenzylamide **518355-76-5P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (thiophen-3-ylmethyl)amide **518355-77-6P 518355-78-7P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (1-methyl-1H-benzimidazol-2-ylmethyl)amide **518355-79-8P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 3-methylbenzylamide **518355-80-1P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 3-chlorobenzylamide **518355-81-2P**, 2-(1H-Indazol-3-yl)-3H-benzimidazole-4-carboxylic acid 4-sulfamoylbenzylamide **518355-82-3P**, 2-(1H-Indazol-3-yl)-3H-benzimidazole-4-carboxylic acid (3-ethoxypropyl)amide **518355-83-4P**, 2-(1H-Indazol-3-yl)-3H-benzimidazole-4-carboxylic acid 4-bromobenzylamide **518355-84-5P**, 2-(1H-Indazol-3-yl)-3H-benzimidazole-4-carboxylic acid (naphthalen-1-ylmethyl)amide **518355-85-6P**, 2-(1H-Indazol-3-yl)-3H-benzimidazole-4-carboxylic acid (thiophen-2-ylmethyl)amide **518355-86-7P**, 2-(1H-Indazol-3-yl)-3H-benzimidazole-4-carboxylic acid 4-dimethylaminobenzylamide **518355-87-8P**, 2-(1H-Indazol-3-yl)-3H-benzimidazole-4-carboxylic acid 4-nitrobenzylamide **518355-88-9P**, 2-(1H-Indazol-3-yl)-3H-benzimidazole-4-carboxylic acid (pyridin-3-ylmethyl)amide **518355-89-0P**, 2-(1H-Indazol-3-yl)-3H-benzimidazole-4-carboxylic acid 3-bromobenzylamide **518355-90-3P**, 2-(1H-Indazol-3-yl)-3H-benzimidazole-4-carboxylic acid 3-methoxybenzylamide **518355-91-4P**, 2-(1H-Indazol-3-yl)-3H-benzimidazole-4-carboxylic acid (benzo[b]thiophen-3-ylmethyl)amide **518355-92-5P**, 2-(1H-Indazol-3-yl)-3H-benzimidazole-4-carboxylic acid 4-phenoxybenzylamide **518355-93-6P**, 2-(1H-Indazol-3-yl)-3H-benzimidazole-4-carboxylic acid 3-trifluoromethoxybenzylamide **518355-94-7P**, 2-(1H-Indazol-3-yl)-3H-benzimidazole-4-carboxylic acid (6-chloropyridin-3-ylmethyl)amide **518355-95-8P**, 2-(1H-Indazol-3-yl)-3H-benzimidazole-4-carboxylic acid

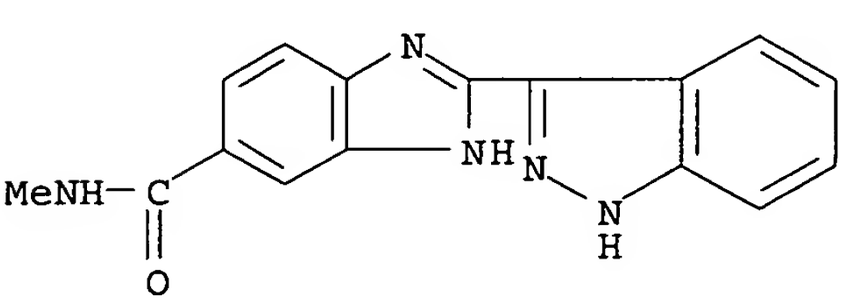
(2,3-dihydrobenzofuran-5-ylmethyl)amide **518355-96-9P**, 2-(1H-Indazol-3-yl)-3H-benzimidazole-4-carboxylic acid 3-trifluoromethylbenzylamide **518355-97-0P**, 2-(1H-Indazol-3-yl)-3H-benzimidazole-4-carboxylic acid 2-methylsulfanylbenzylamide **518355-98-1P**, 2-(1H-Indazol-3-yl)-3H-benzimidazole-4-carboxylic acid (furan-3-ylmethyl)amide **518355-99-2P**, 2-(1H-Indazol-3-yl)-3H-benzimidazole-4-carboxylic acid 2-nitrobenzylamide **518356-00-8P** **518356-01-9P**, 2-(1H-Indazol-3-yl)-3H-benzimidazole-4-carboxylic acid 3-chlorobenzylamide **518356-02-0P**, 2-(1H-Indazol-3-yl)-3H-benzimidazole-4-carboxylic acid phenylamide **518356-03-1P**, 2-(1H-Indazol-3-yl)-3H-benzimidazole-4-carboxylic acid benzylamide **518356-04-2P**, 2-(1H-Indazol-3-yl)-3H-benzimidazole-4-carboxylic acid phenethylamide **518356-53-1P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid [(5-methoxy-4-oxo-4H-pyran-2-yl)methyl]amide **518356-54-2P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-acetylaminobenzylamide **518356-55-3P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 3-nitrobenzylamide **518356-56-4P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 2-fluorobenzylamide **518356-57-5P** **518356-58-6P** **518356-59-7P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-bromo-2-fluorobenzylamide **518356-60-0P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-chloro-2-fluorobenzylamide **518356-61-1P** **518356-62-2P** **518356-63-3P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (4'-chlorobiphenyl-4-ylmethyl)amide **518356-64-4P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid [(3',5'-dichlorobiphenyl-4-yl)methyl]amide **518356-65-5P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid [(4'-fluorobiphenyl-4-yl)methyl]amide **518356-66-6P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 2,6-difluoro-3-methylbenzylamide **518356-67-7P** **518356-68-8P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-chlorobenzylamide **518356-69-9P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-chloro-2-methylbenzylamide **518356-70-2P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-fluorobenzylamide **518356-71-3P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid [(2'-chlorobiphenyl-4-yl)methyl]amide **518356-72-4P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (6-trifluoromethylpyridin-3-ylmethyl)amide **518356-73-5P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (5-(pyridin-2-yl)thiophen-2-ylmethyl)amide **518356-74-6P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (3-imidazol-1-ylpropyl)amide **518356-75-7P**, 4-[2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carbonyl]piperazine-1-carboxylic acid tert-butyl ester **518356-76-8P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (2,6-difluoro-4-chlorobenzyl)amide **518356-77-9P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (2,4-dichloro-6-fluorobenzyl)amide **518356-78-0P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (3-fluoro-4-chlorobenzyl)amide **518356-79-1P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (2-fluoro-4-chloro-6-methylbenzyl)amide **518356-80-4P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (6-methoxypyridin-3-ylmethyl)amide **518987-99-0P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-sulfonic acid benzylamide **518988-03-9P**, 2-(Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid dimethylamide **518988-07-3P**, 2-[4-(Isopropylcarbamoyl)-1H-pyrazol-3-yl]-1H-benzimidazole-5-carboxylic acid (pyridin-3-ylmethyl)amide **518988-11-9P**, 2-[4-(Isopropylcarbamoyl)-1H-pyrazol-3-yl]-1H-

benzimidazole-5-carboxylic acid (phenylmethyl)amide **518988-12-0P**, 2-[4-(Isopropylcarbamoyl)-1H-pyrazol-3-yl]-1H-benzimidazole-5-carboxylic acid (pyridin-2-ylmethyl)amide **518988-13-1P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-methylbenzylamide **518988-14-2P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid [3-(2-oxopyrrolidin-1-yl)propyl]amide **518988-15-3P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (2-morpholinoethyl)amide **518988-17-5P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (2-methoxyethyl)amide **518988-19-7P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (2-hydroxy-1,1-dimethylethyl)amide **518988-25-5P**, 2-(4-Isobutyrylamino-1H-pyrazol-3-yl)-1H-benzimidazole-5-carboxylic acid benzylamide **518988-27-7P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (2-piperidin-1-ylethyl)amide **518988-28-8P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (pyridin-2-ylmethyl)amide **518988-29-9P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid [3-(4-methylpiperazin-1-yl)propyl]amide **518989-46-3P**, 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid [2-(2H-tetrazol-5-yl)ethyl]amide
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of benzimidazoles and analogs and their use as protein kinase inhibitors)

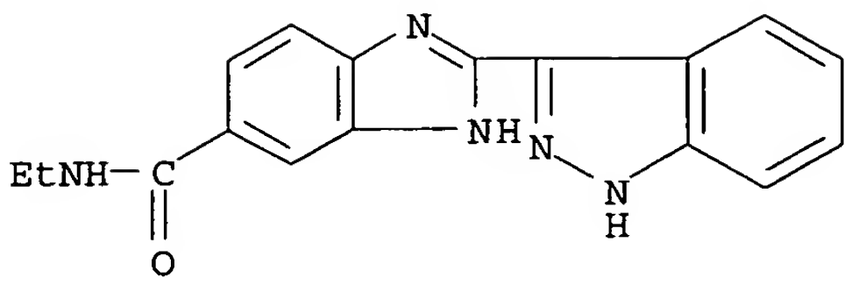
RN 518355-10-7 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, 2-(1H-indazol-3-yl)-N-(phenylmethyl)- (9CI) (CA INDEX NAME)



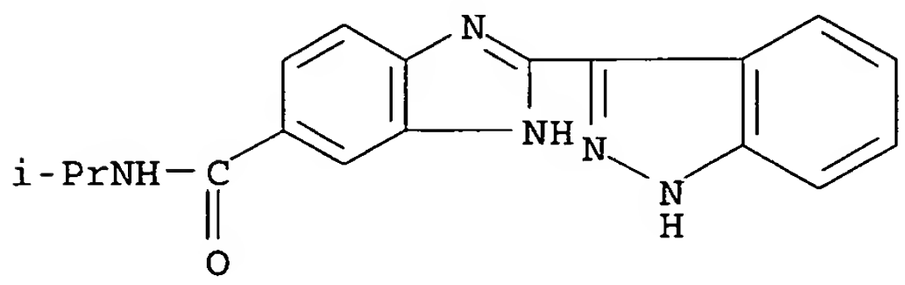
RN 518355-11-8 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, 2-(1H-indazol-3-yl)-N-methyl- (9CI) (CA INDEX NAME)



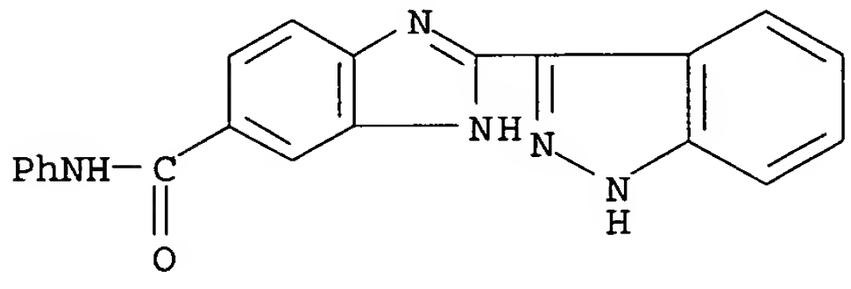
RN 518355-12-9 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-ethyl-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



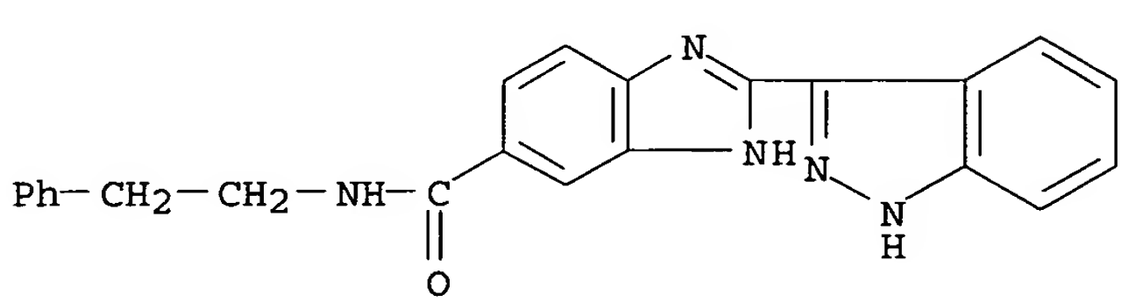
RN 518355-13-0 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, 2-(1H-indazol-3-yl)-N-(1-methylethyl)-(9CI) (CA INDEX NAME)



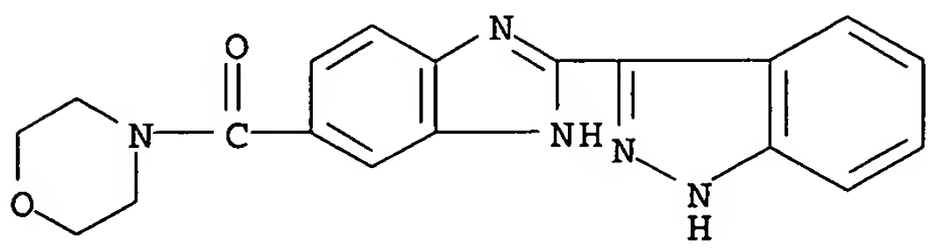
RN 518355-14-1 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, 2-(1H-indazol-3-yl)-N-phenyl- (9CI) (CA INDEX NAME)



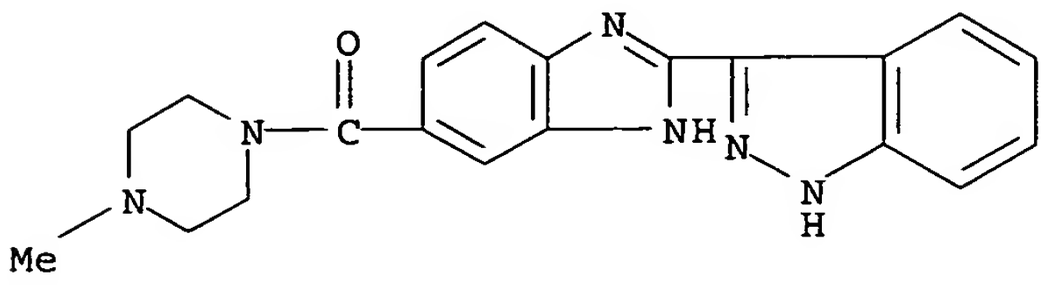
RN 518355-15-2 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, 2-(1H-indazol-3-yl)-N-(2-phenylethyl)-(9CI) (CA INDEX NAME)



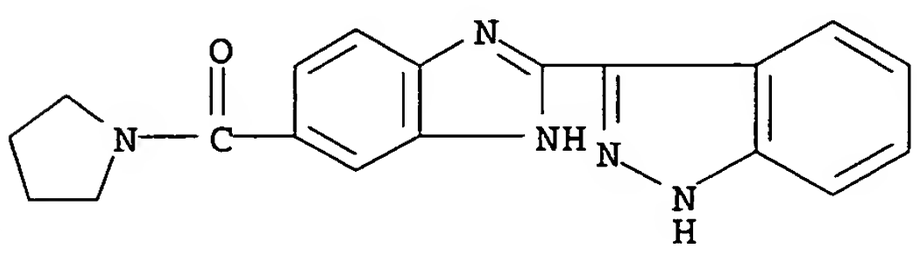
RN 518355-16-3 HCAPLUS
CN Morpholine, 4-[[2-(1H-indazol-3-yl)-1H-benzimidazol-5-yl]carbonyl]- (9CI) (CA INDEX NAME)



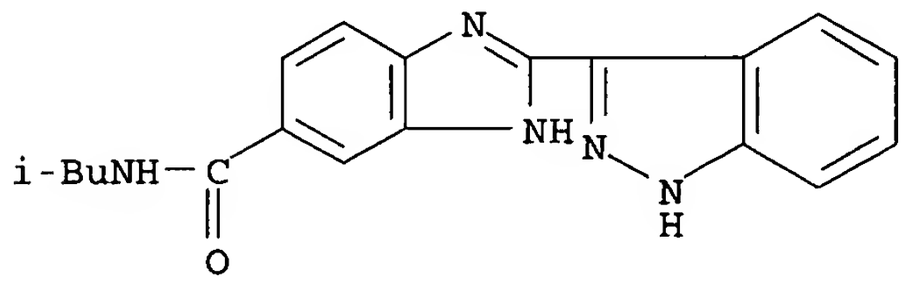
RN 518355-17-4 HCAPLUS
CN Piperazine, 1-[[2-(1H-indazol-3-yl)-1H-benzimidazol-5-yl]carbonyl]-4-methyl- (9CI) (CA INDEX NAME)



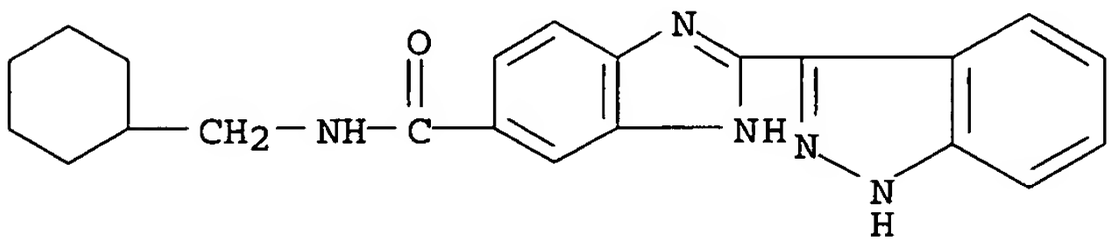
RN 518355-18-5 HCAPLUS
CN Pyrrolidine, 1-[[2-(1H-indazol-3-yl)-1H-benzimidazol-5-yl]carbonyl]- (9CI) (CA INDEX NAME)



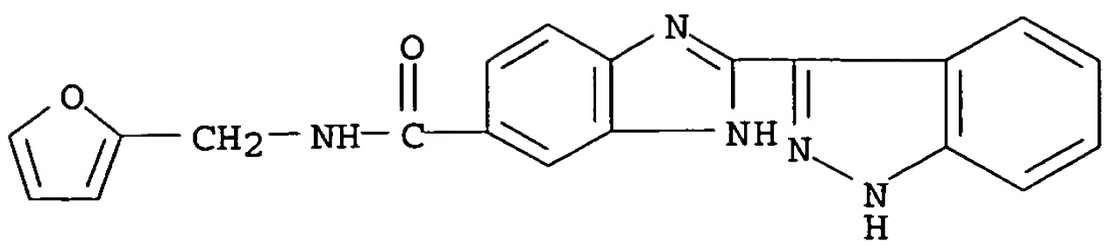
RN 518355-19-6 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, 2-(1H-indazol-3-yl)-N-(2-methylpropyl)-(9CI) (CA INDEX NAME)



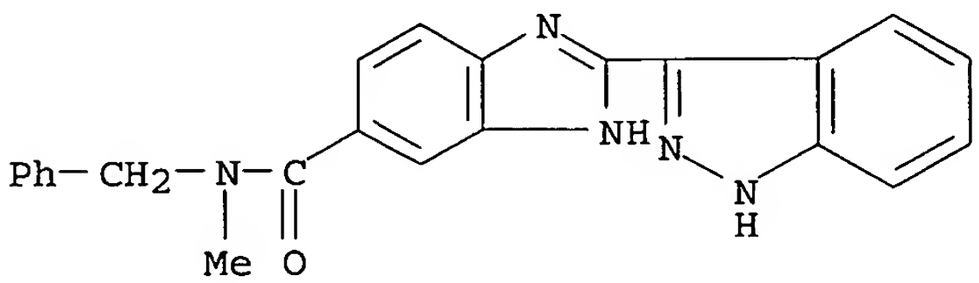
RN 518355-20-9 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-(cyclohexylmethyl)-2-(1H-indazol-3-yl)-(9CI) (CA INDEX NAME)



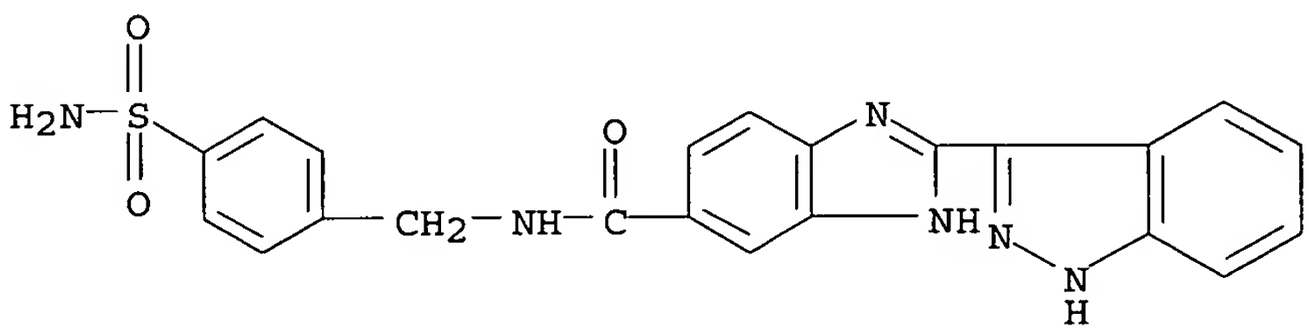
RN 518355-22-1 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-(2-furanylmethyl)-2-(1H-indazol-3-yl)-(9CI) (CA INDEX NAME)



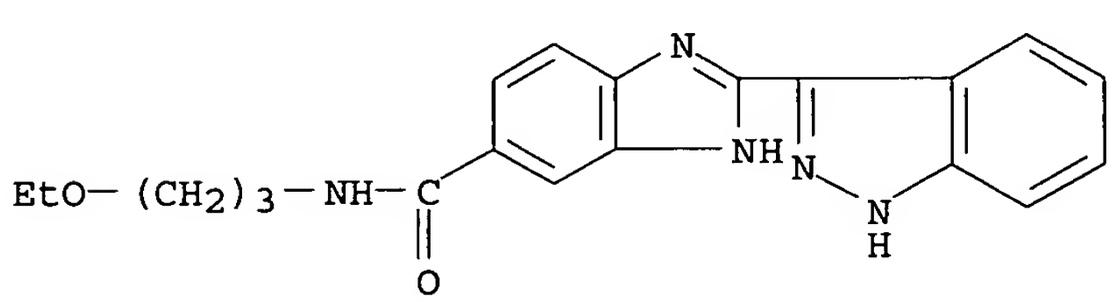
RN 518355-23-2 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, 2-(1H-indazol-3-yl)-N-methyl-N-(phenylmethyl)- (9CI) (CA INDEX NAME)



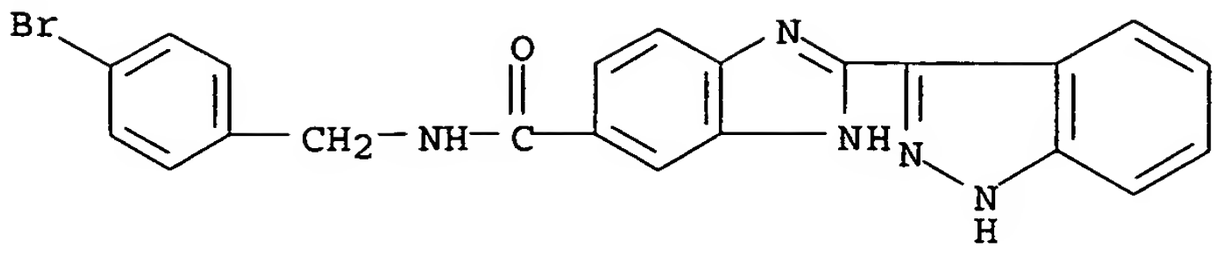
RN 518355-36-7 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[[4-(aminosulfonyl)phenyl]methyl]-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



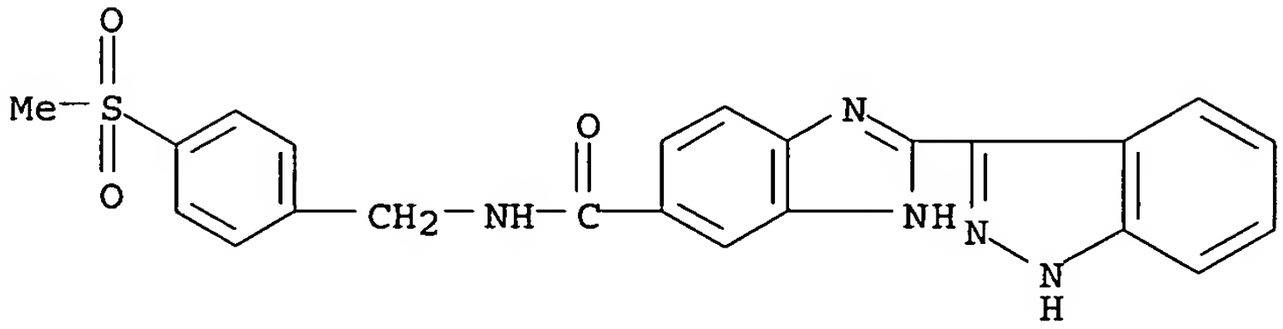
RN 518355-37-8 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-(3-ethoxypropyl)-2-(1H-indazol-3-yl)-(9CI) (CA INDEX NAME)



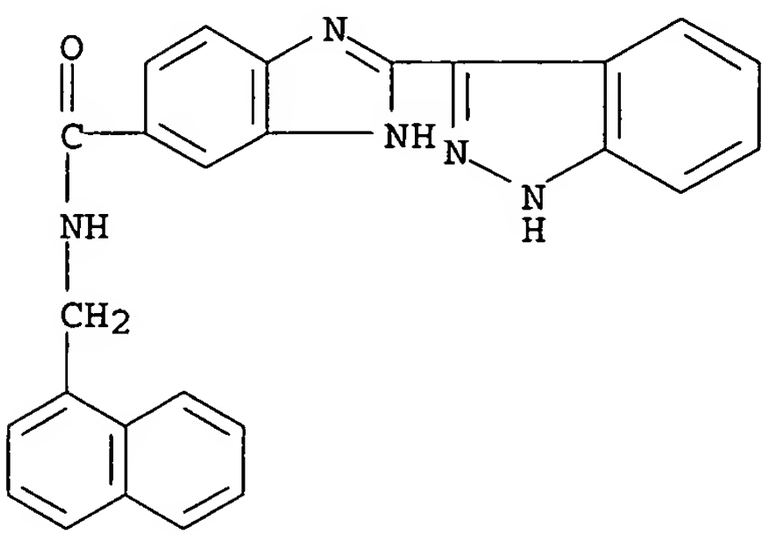
RN 518355-38-9 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(4-bromophenyl)methyl]-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



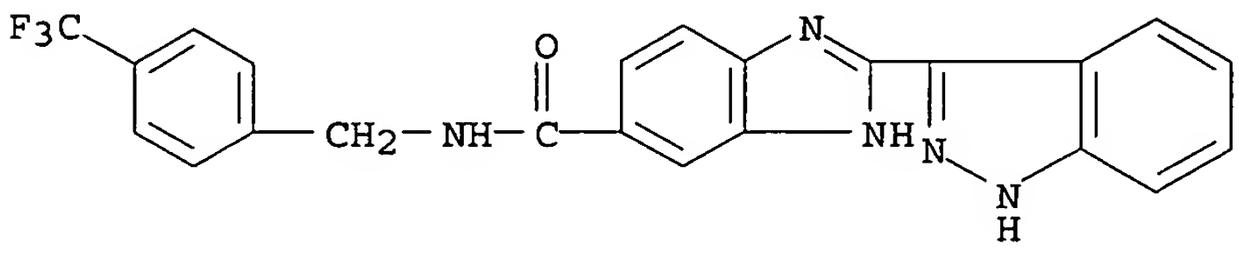
RN 518355-39-0 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, 2-(1H-indazol-3-yl)-N-[[4-(methylsulfonyl)phenyl]methyl]- (9CI) (CA INDEX NAME)



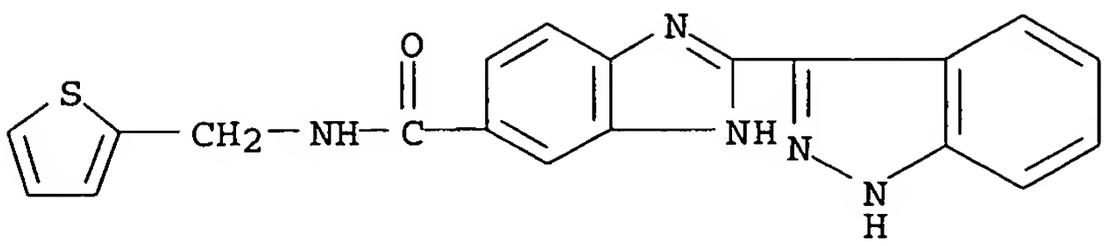
RN 518355-40-3 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, 2-(1H-indazol-3-yl)-N-(1-naphthalenylmethyl)- (9CI) (CA INDEX NAME)



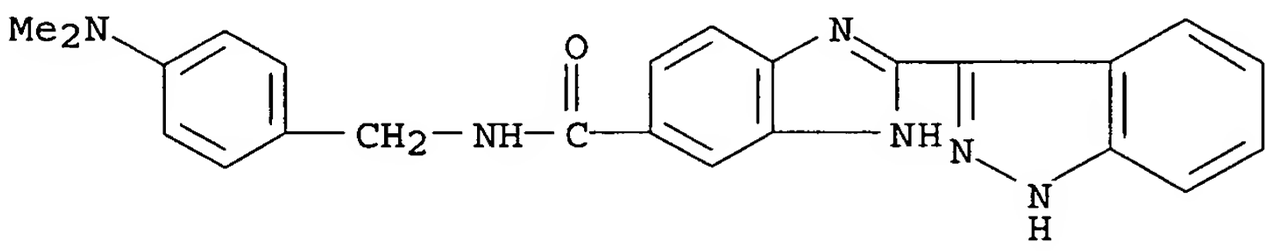
RN 518355-41-4 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, 2-(1H-indazol-3-yl)-N-[[4-(trifluoromethyl)phenyl]methyl]- (9CI) (CA INDEX NAME)



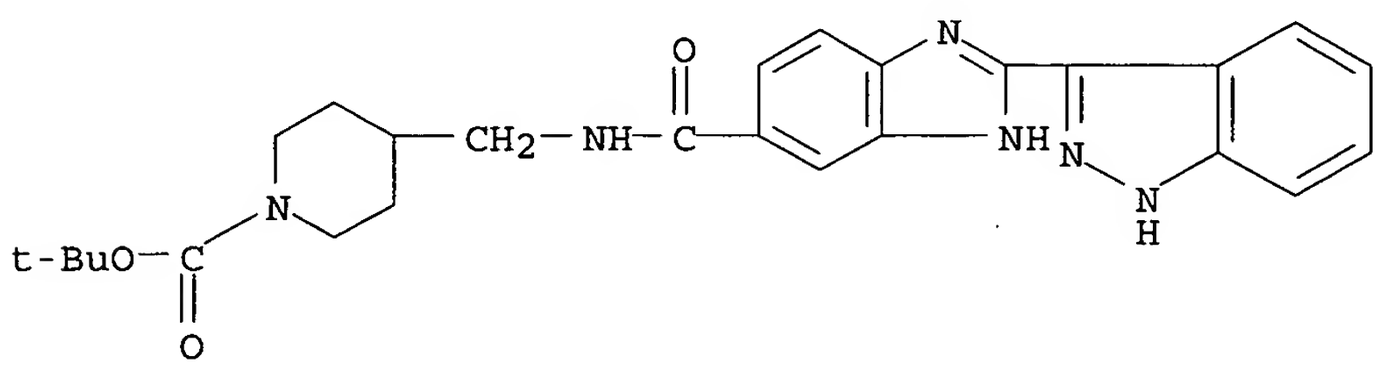
RN 518355-42-5 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, 2-(1H-indazol-3-yl)-N-(2-thienylmethyl)- (9CI) (CA INDEX NAME)



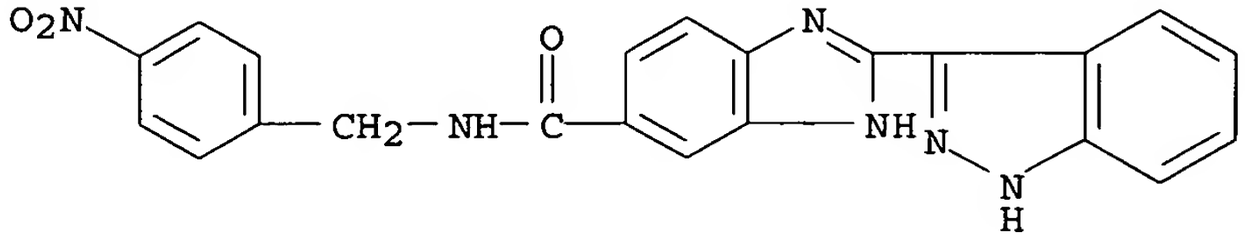
RN 518355-43-6 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[[4-(dimethylamino)phenyl]methyl]-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



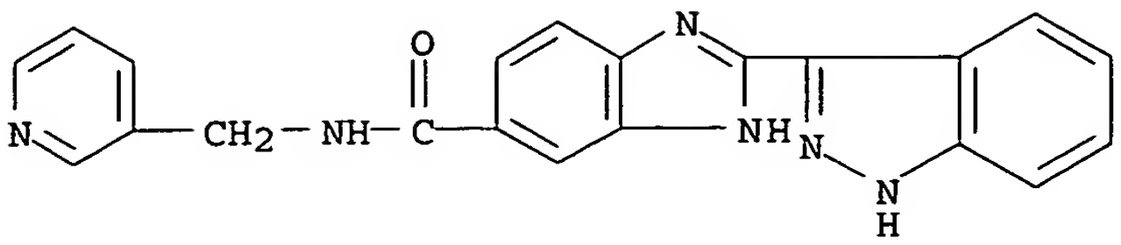
RN 518355-44-7 HCAPLUS
CN 1-Piperidinecarboxylic acid, 4-[[[[2-(1H-indazol-3-yl)-1H-benzimidazol-5-yl]carbonyl]amino]methyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



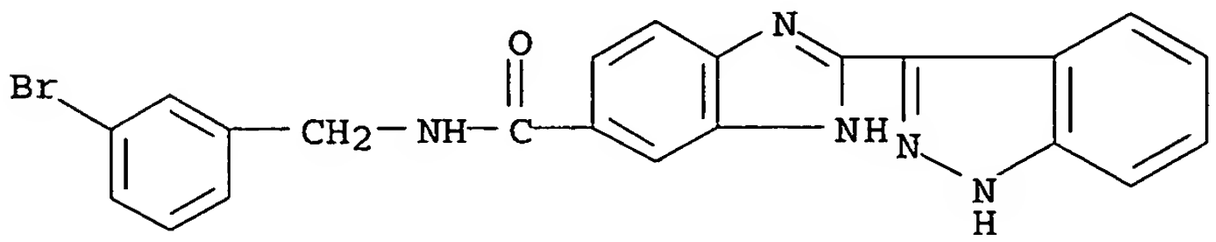
RN 518355-45-8 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, 2-(1H-indazol-3-yl)-N-[(4-nitrophenyl)methyl]- (9CI) (CA INDEX NAME)



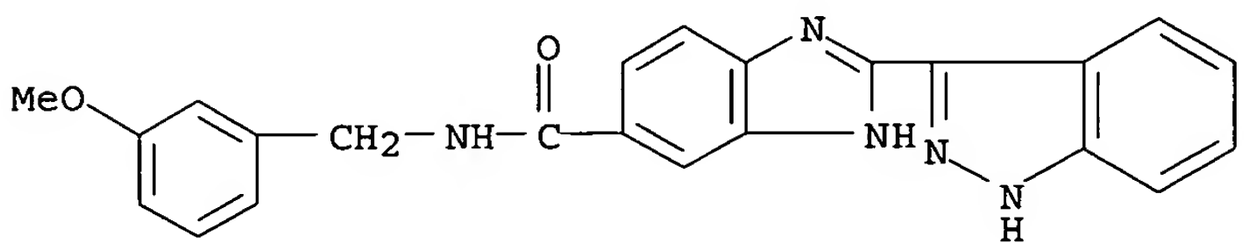
RN 518355-46-9 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, 2-(1H-indazol-3-yl)-N-(3-pyridinylmethyl)- (9CI) (CA INDEX NAME)



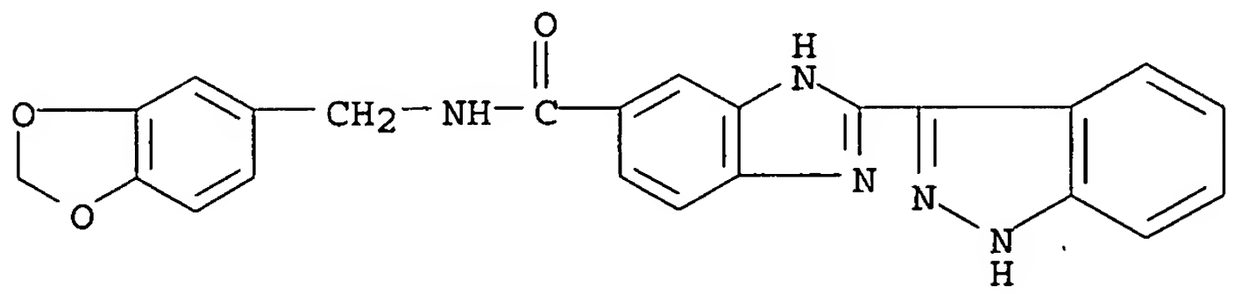
RN 518355-47-0 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(3-bromophenyl)methyl]-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



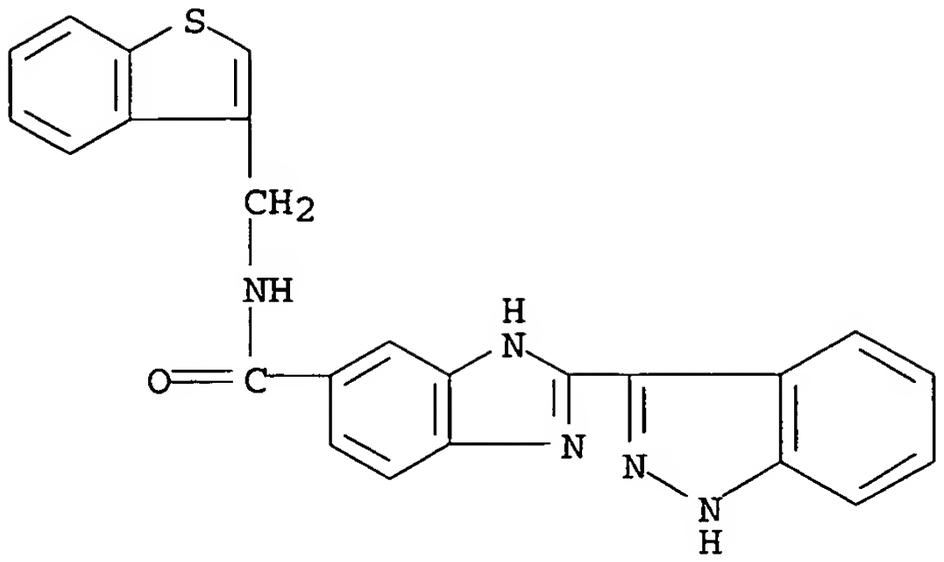
RN 518355-48-1 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, 2-(1H-indazol-3-yl)-N-[(3-methoxyphenyl)methyl]- (9CI) (CA INDEX NAME)



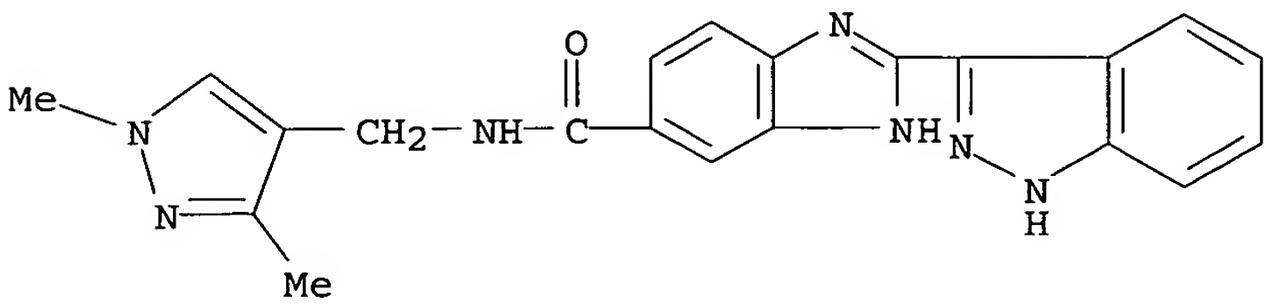
RN 518355-49-2 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-(1,3-benzodioxol-5-ylmethyl)-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



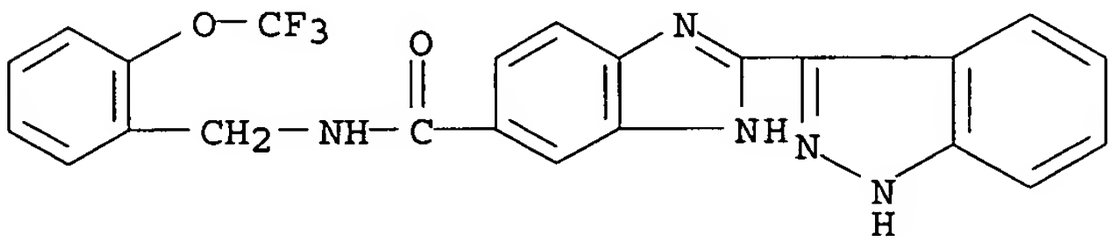
RN 518355-50-5 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-(benzo[b]thien-3-ylmethyl)-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



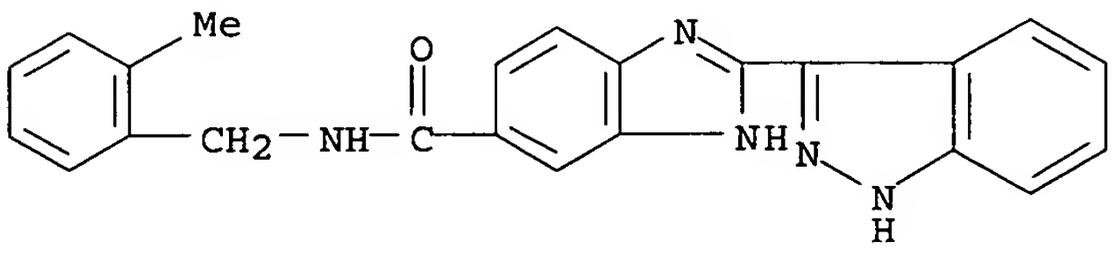
RN 518355-51-6 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1,3-dimethyl-1H-pyrazol-4-yl)methyl]-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



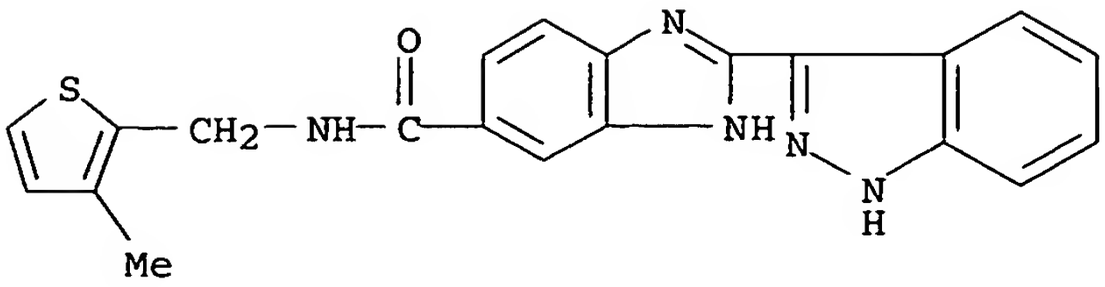
RN 518355-52-7 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, 2-(1H-indazol-3-yl)-N-[[2-(trifluoromethoxy)phenyl]methyl]- (9CI) (CA INDEX NAME)



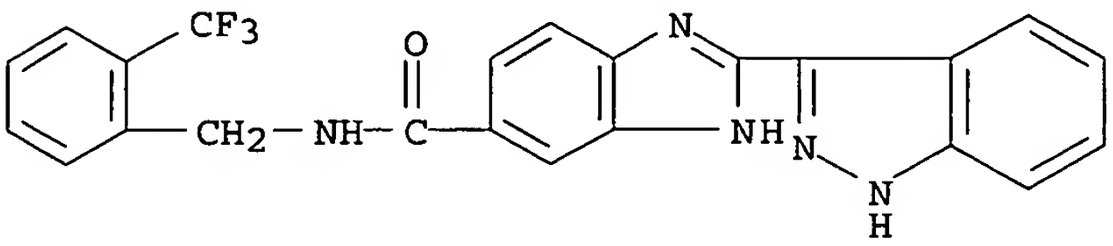
RN 518355-53-8 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, 2-(1H-indazol-3-yl)-N-[(2-methylphenyl)methyl]- (9CI) (CA INDEX NAME)



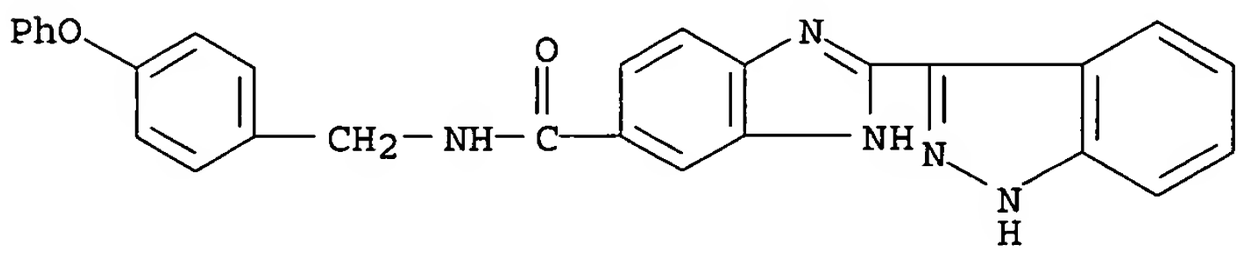
RN 518355-54-9 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, 2-(1H-indazol-3-yl)-N-[(3-methyl-2-thienyl)methyl]- (9CI) (CA INDEX NAME)



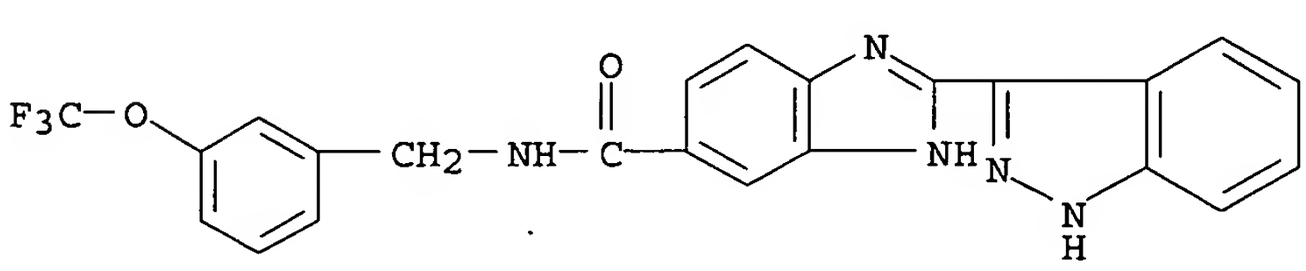
RN 518355-56-1 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, 2-(1H-indazol-3-yl)-N-[[2-(trifluoromethyl)phenyl]methyl]- (9CI) (CA INDEX NAME)



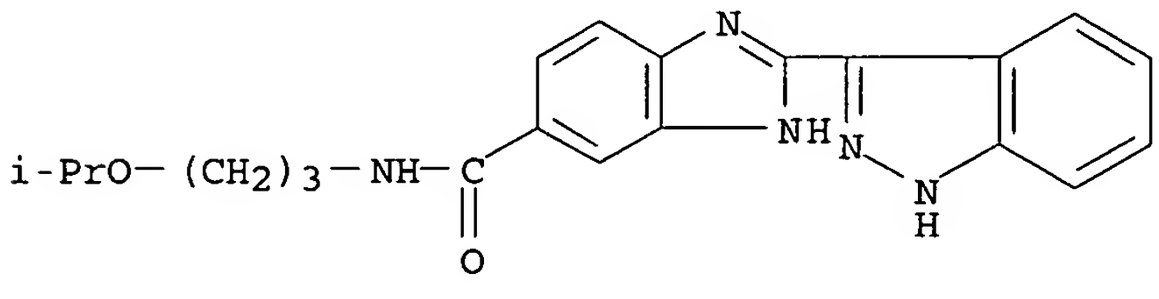
RN 518355-57-2 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, 2-(1H-indazol-3-yl)-N-[(4-phenoxyphenyl)methyl]- (9CI) (CA INDEX NAME)



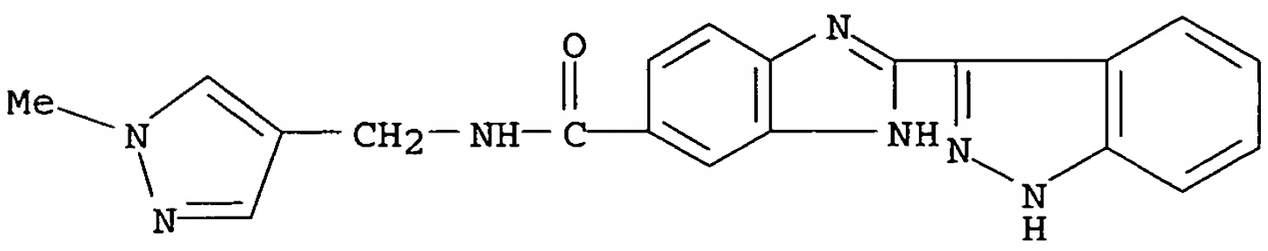
RN 518355-58-3 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, 2-(1H-indazol-3-yl)-N-[[3-(trifluoromethoxy)phenyl]methyl]- (9CI) (CA INDEX NAME)



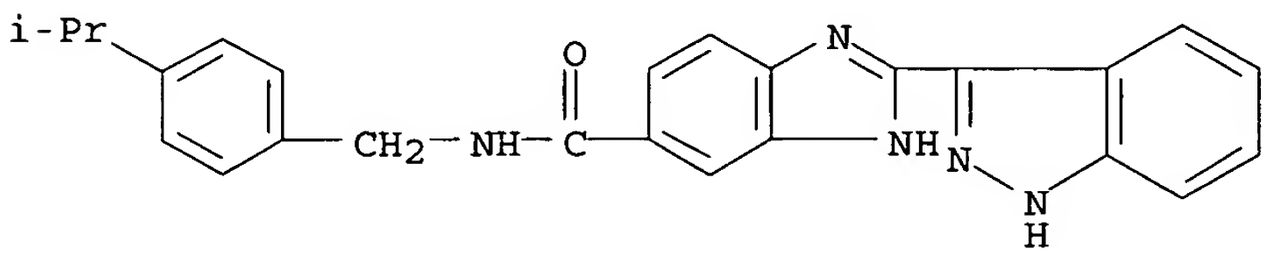
RN 518355-59-4 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, 2-(1H-indazol-3-yl)-N-[3-(1-methylethoxy)propyl]- (9CI) (CA INDEX NAME)



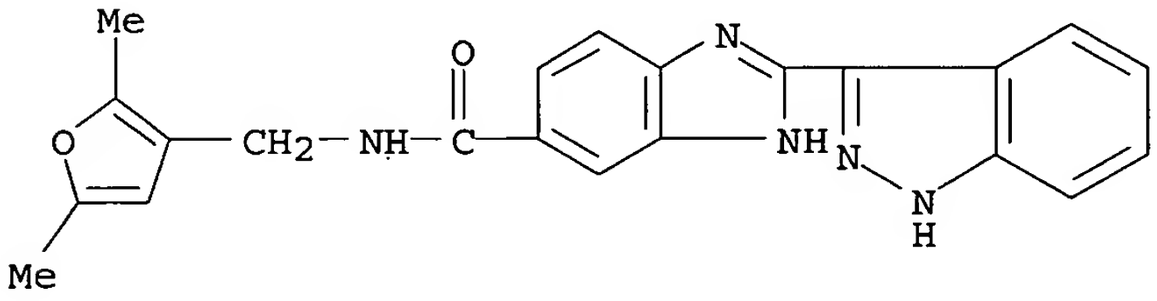
RN 518355-60-7 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, 2-(1H-indazol-3-yl)-N-[(1-methyl-1H-pyrazol-4-yl)methyl]- (9CI) (CA INDEX NAME)



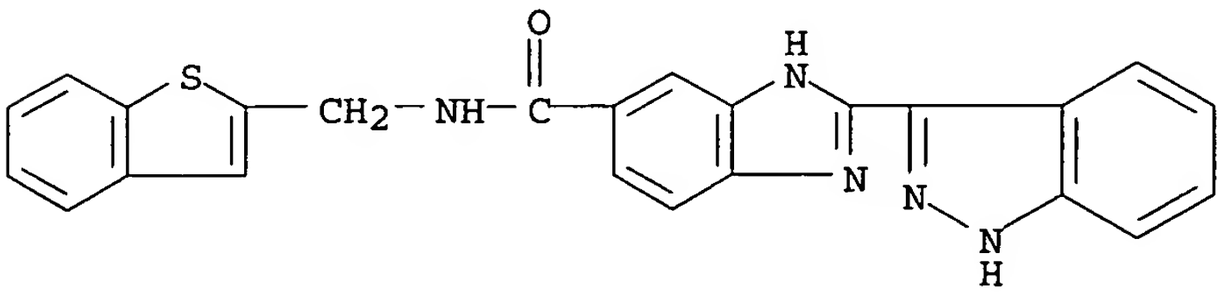
RN 518355-61-8 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, 2-(1H-indazol-3-yl)-N-[[4-(1-methylethyl)phenyl]methyl]- (9CI) (CA INDEX NAME)



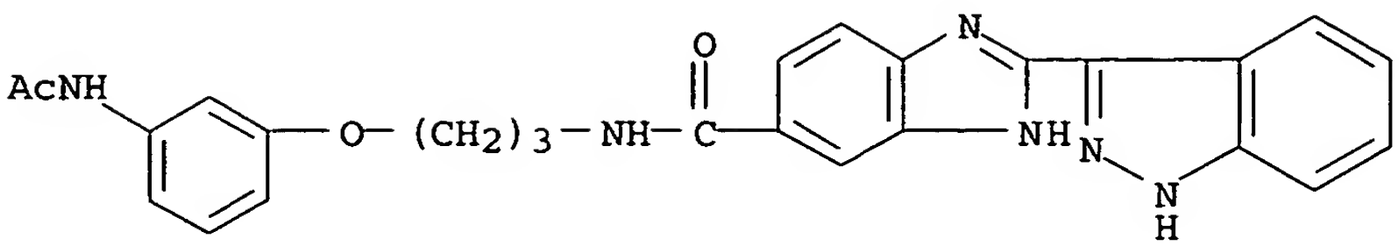
RN 518355-62-9 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(2,5-dimethyl-3-furanyl)methyl]-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



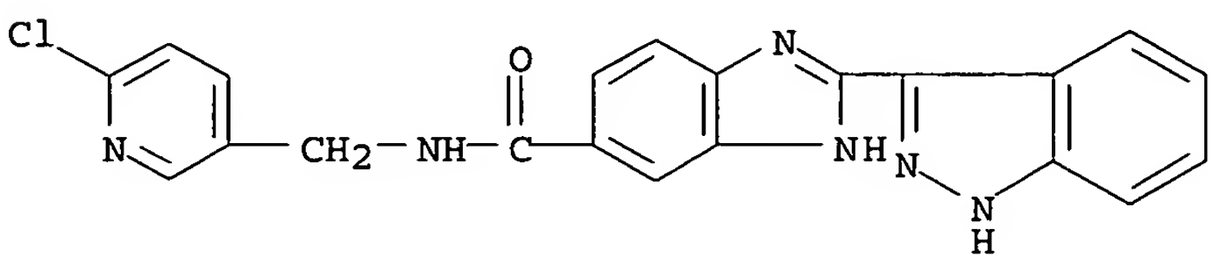
RN 518355-63-0 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-(benzo[b]thien-2-ylmethyl)-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



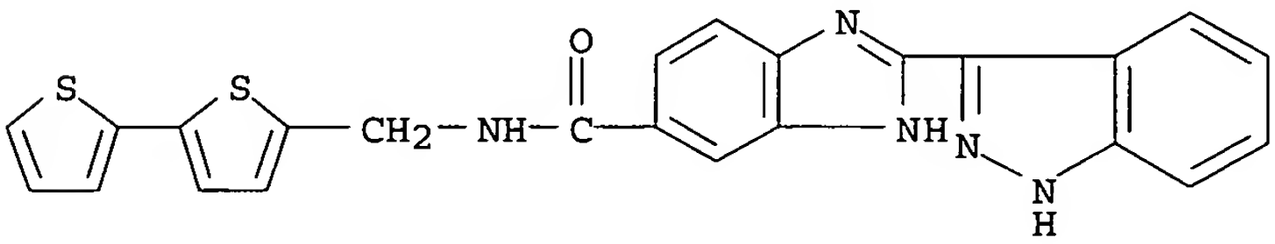
RN 518355-64-1 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[3-[3-(acetylamino)phenoxy]propyl]-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



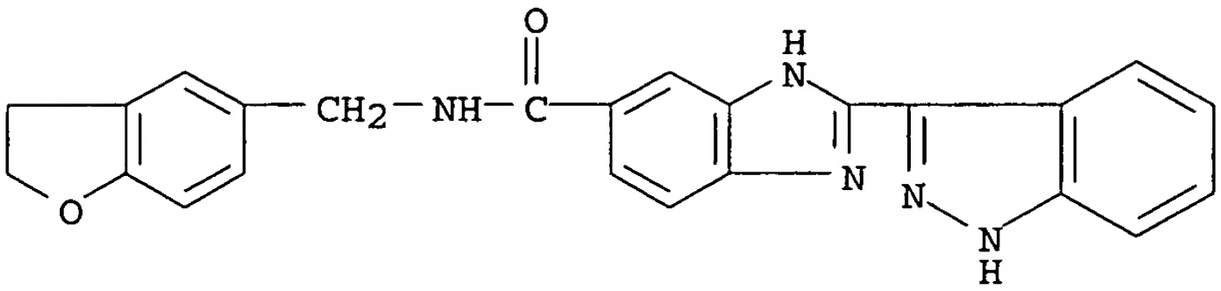
RN 518355-65-2 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(6-chloro-3-pyridinyl)methyl]-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



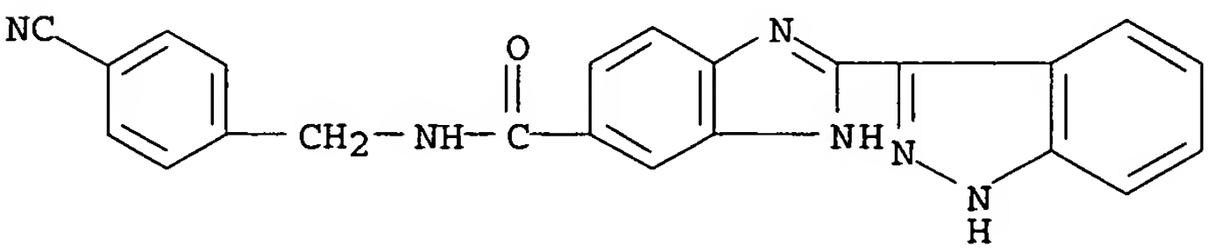
RN 518355-66-3 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-([2,2'-bithiophen]-5-ylmethyl)-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



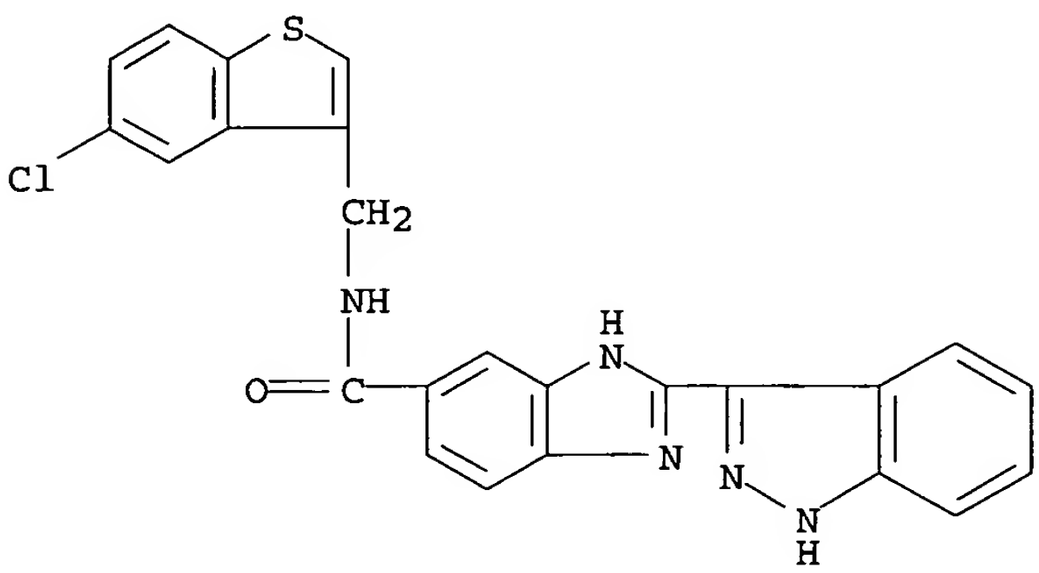
RN 518355-67-4 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(2,3-dihydro-5-benzofuranyl)methyl]-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



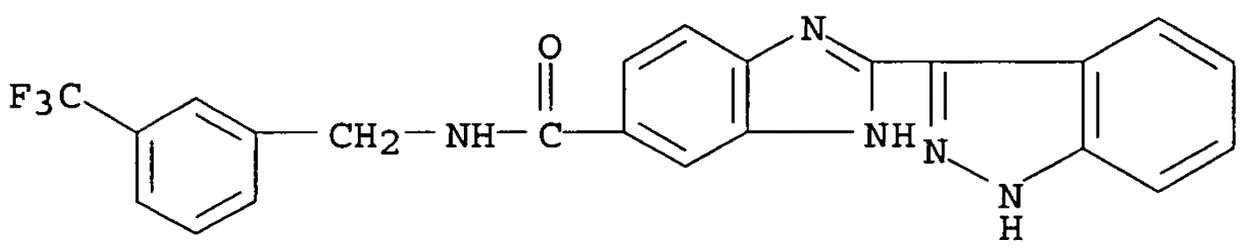
RN 518355-68-5 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(4-cyanophenyl)methyl]-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



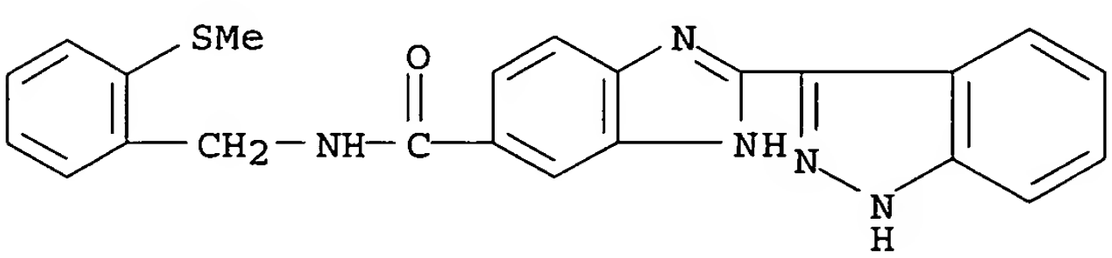
RN 518355-69-6 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(5-chlorobenzo[b]thien-3-yl)methyl]-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



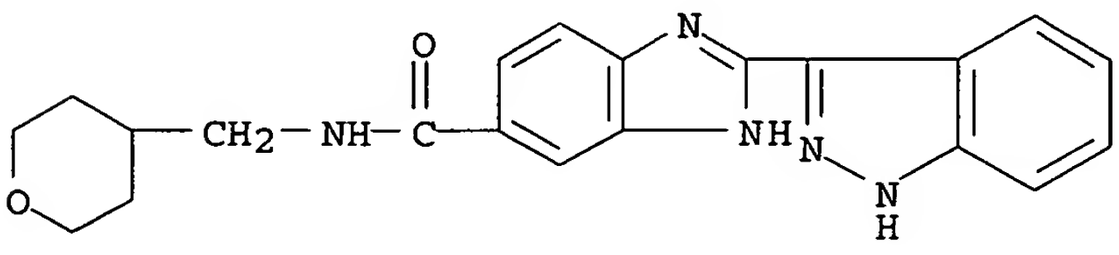
RN 518355-70-9 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, 2-(1H-indazol-3-yl)-N-[[3-(trifluoromethyl)phenyl]methyl]- (9CI) (CA INDEX NAME)



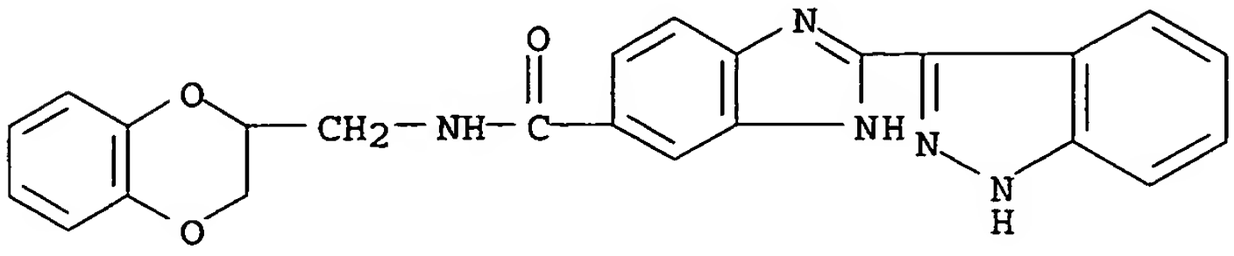
RN 518355-71-0 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, 2-(1H-indazol-3-yl)-N-[[2-(methylthio)phenyl]methyl]- (9CI) (CA INDEX NAME)



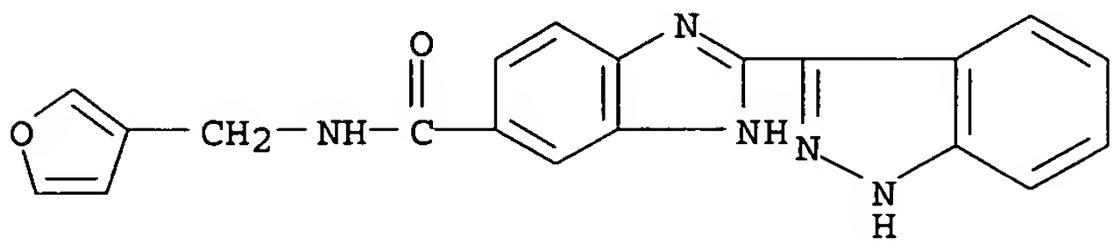
RN 518355-72-1 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, 2-(1H-indazol-3-yl)-N-[(tetrahydro-2H-pyran-4-yl)methyl]- (9CI) (CA INDEX NAME)



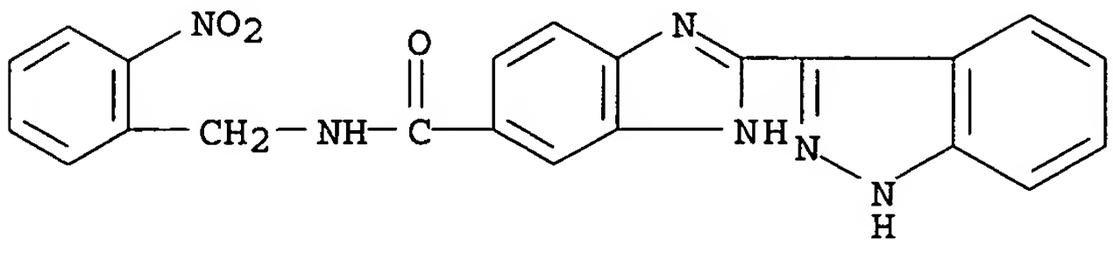
RN 518355-73-2 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(2,3-dihydro-1,4-benzodioxin-2-yl)methyl]-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



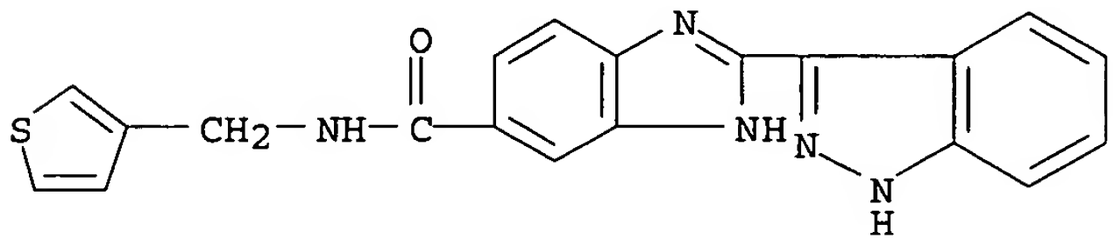
RN 518355-74-3 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-(3-furanylmethyl)-2-(1H-indazol-3-yl)-(9CI) (CA INDEX NAME)



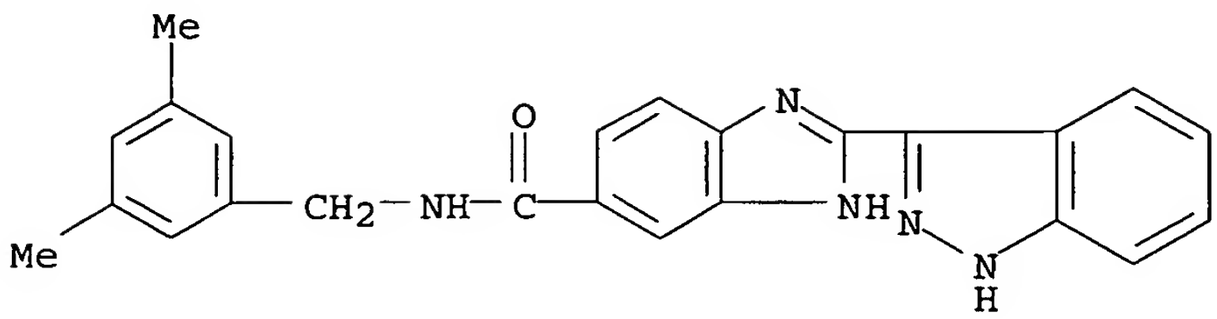
RN 518355-75-4 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, 2-(1H-indazol-3-yl)-N-[(2-nitrophenyl)methyl]- (9CI) (CA INDEX NAME)



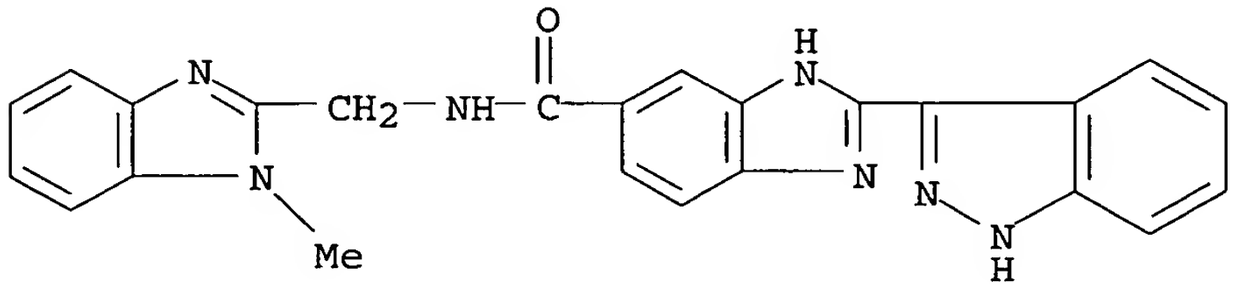
RN 518355-76-5 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, 2-(1H-indazol-3-yl)-N-(3-thienylmethyl)-(9CI) (CA INDEX NAME)



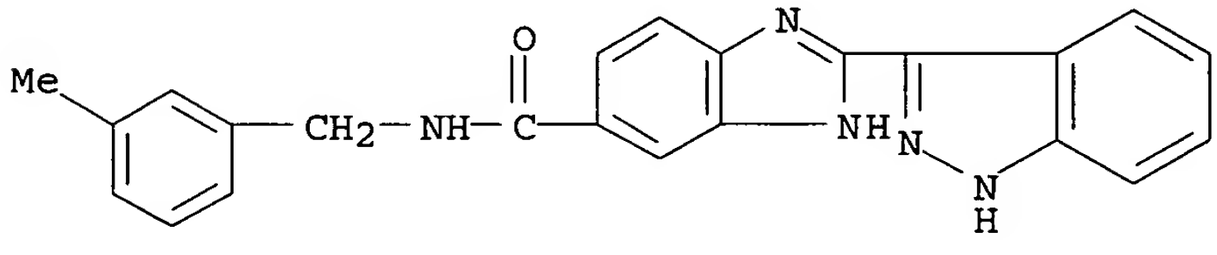
RN 518355-77-6 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(3,5-dimethylphenyl)methyl]-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



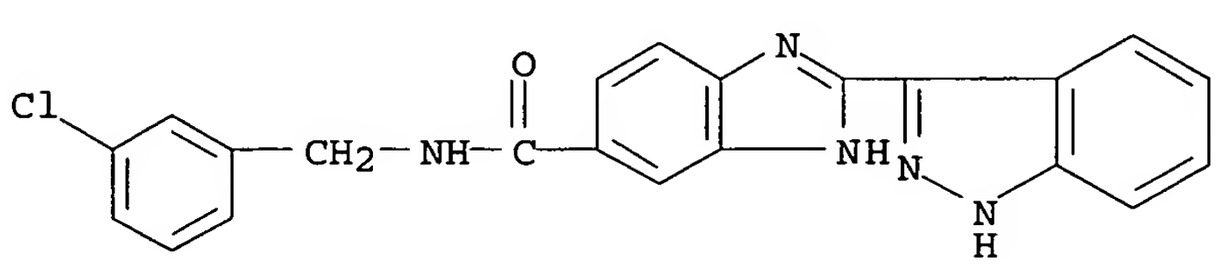
RN 518355-78-7 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, 2-(1H-indazol-3-yl)-N-[(1-methyl-1H-benzimidazol-2-yl)methyl]- (9CI) (CA INDEX NAME)



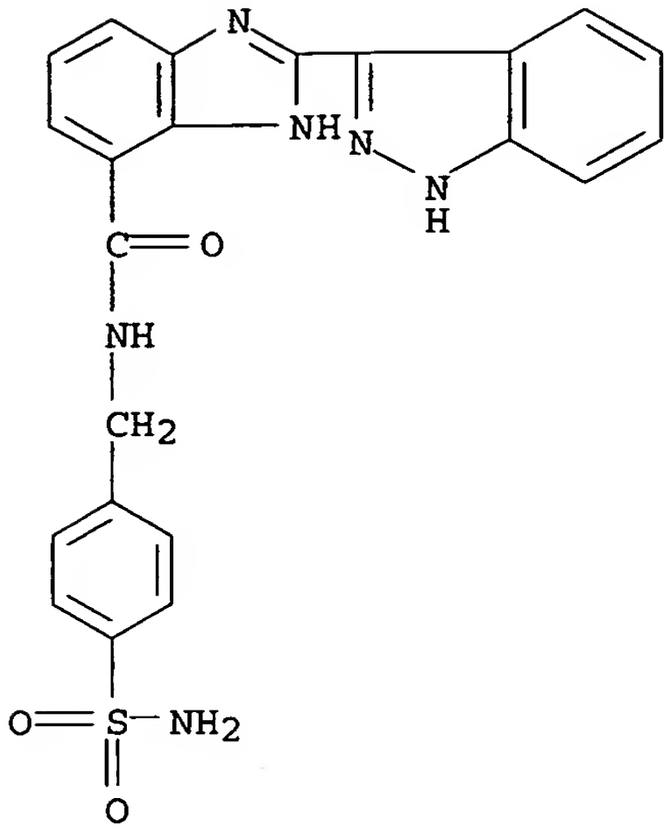
RN 518355-79-8 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, 2-(1H-indazol-3-yl)-N-[(3-methylphenyl)methyl]- (9CI) (CA INDEX NAME)



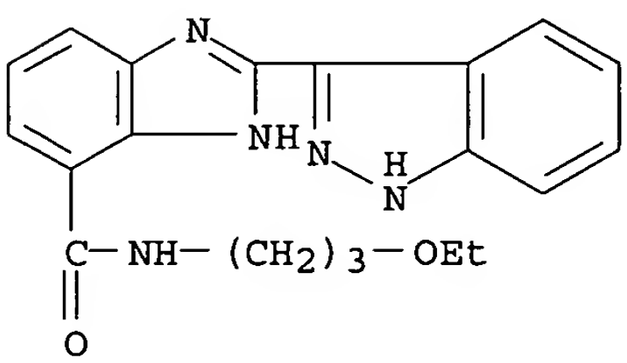
RN 518355-80-1 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(3-chlorophenyl)methyl]-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



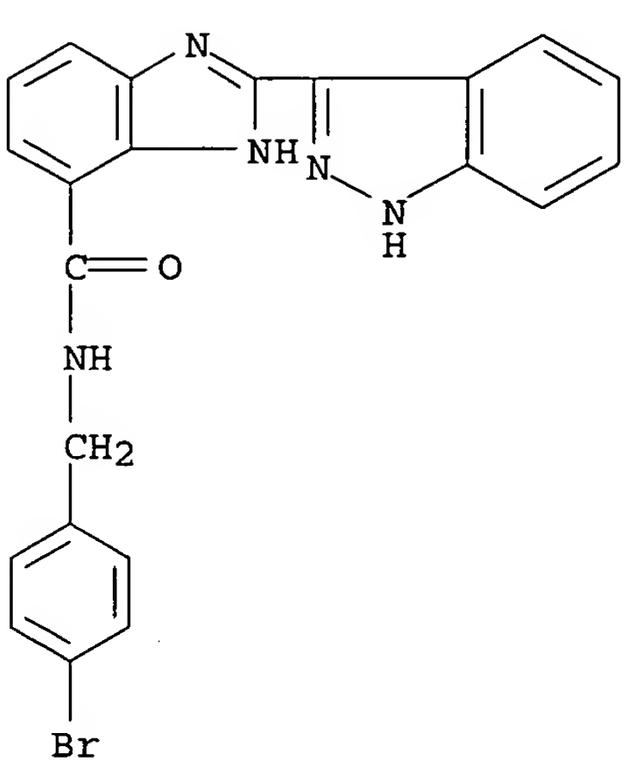
RN 518355-81-2 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[[4-(aminosulfonyl)phenyl]methyl]-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



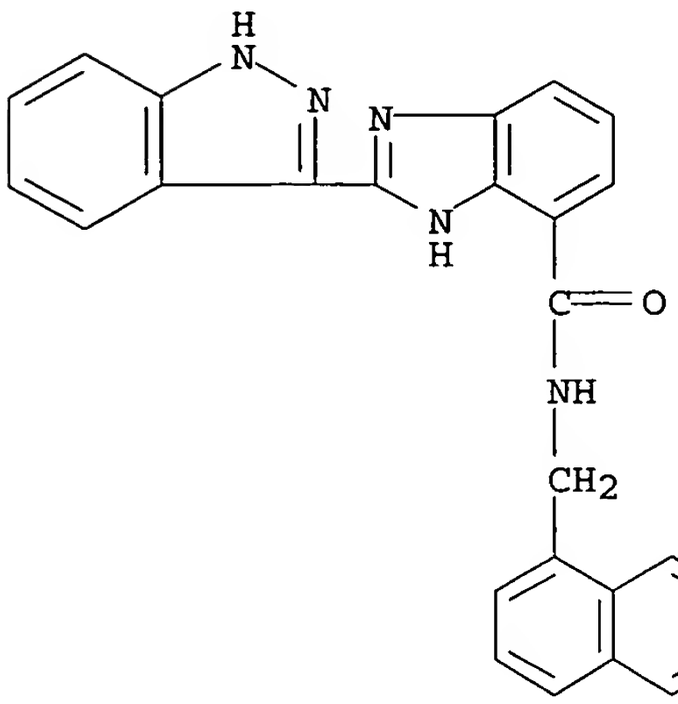
RN 518355-82-3 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-(3-ethoxypropyl)-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



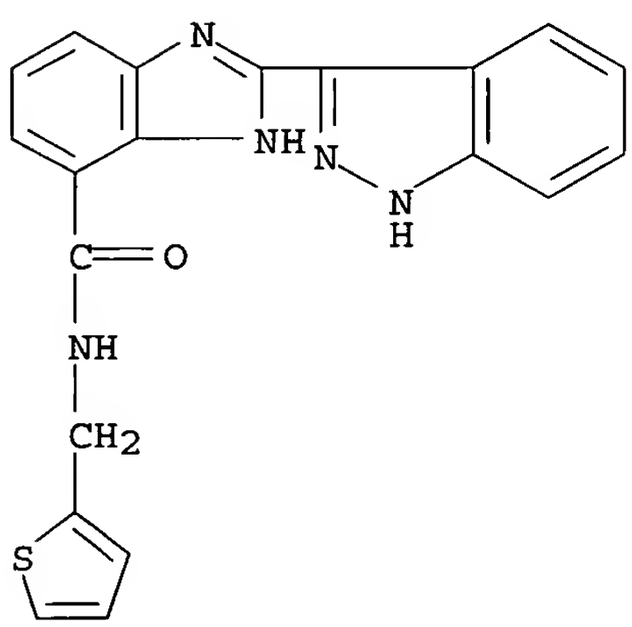
RN 518355-83-4 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(4-bromophenyl)methyl]-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



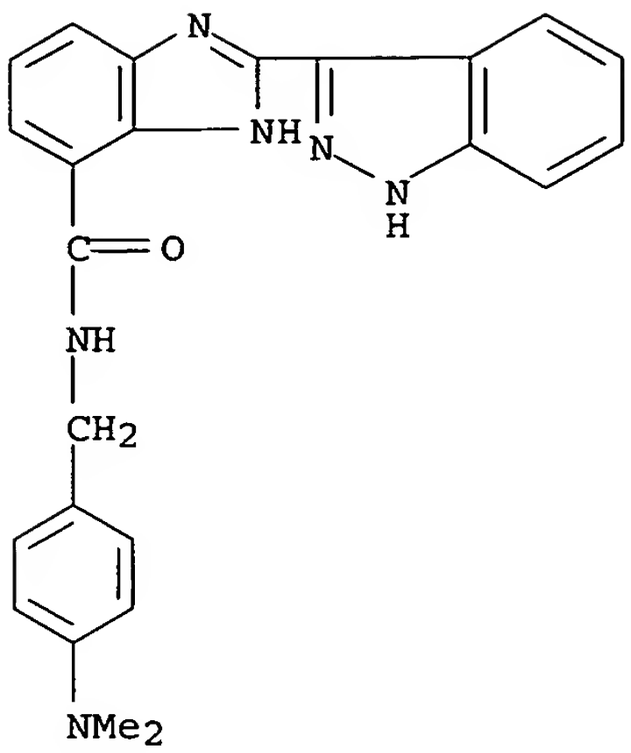
RN 518355-84-5 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, 2-(1H-indazol-3-yl)-N-(1-naphthalenylmethyl)- (9CI) (CA INDEX NAME)



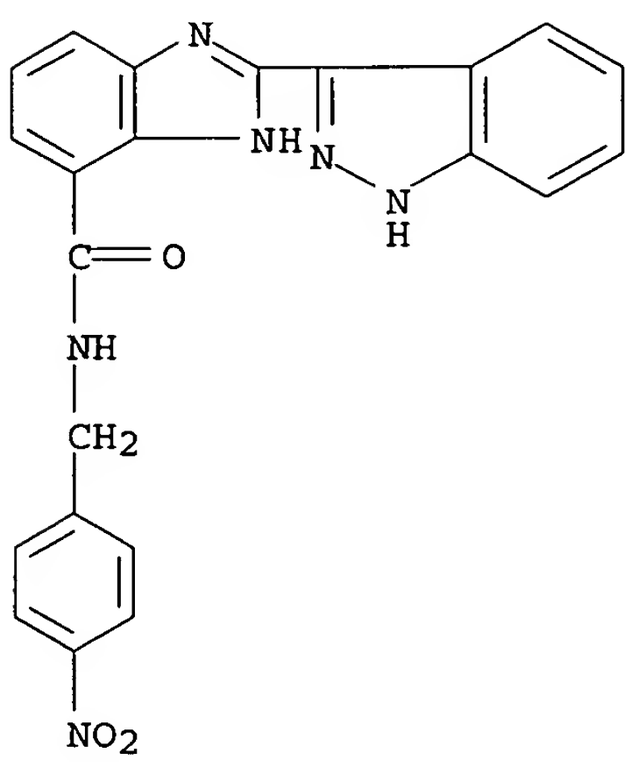
RN 518355-85-6 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, 2-(1H-indazol-3-yl)-N-(2-thienylmethyl)- (9CI) (CA INDEX NAME)



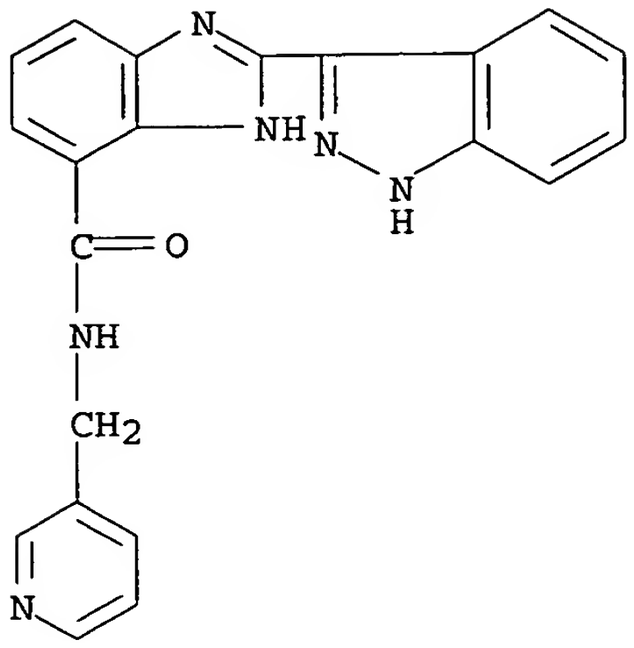
RN 518355-86-7 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[[4-(dimethylamino)phenyl]methyl]-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



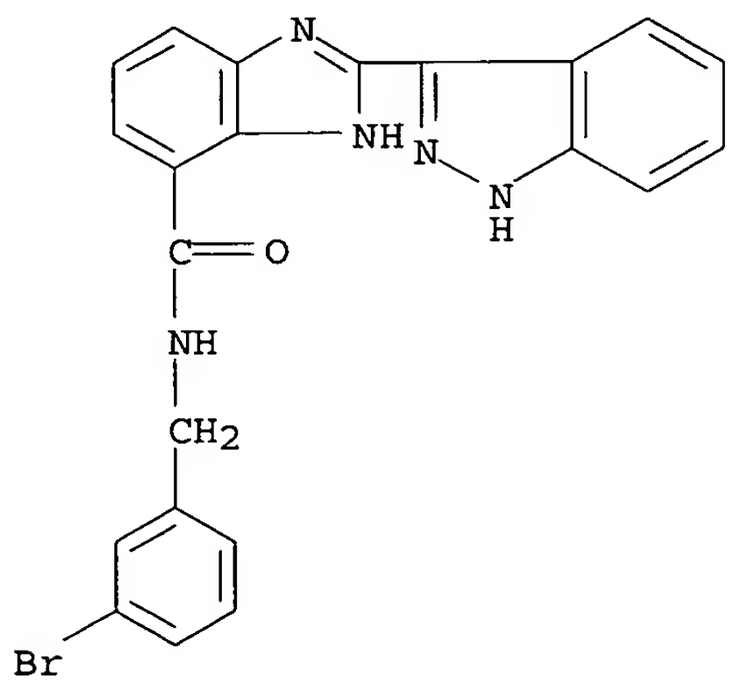
RN 518355-87-8 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, 2-(1H-indazol-3-yl)-N-[(4-nitrophenyl)methyl]- (9CI) (CA INDEX NAME)



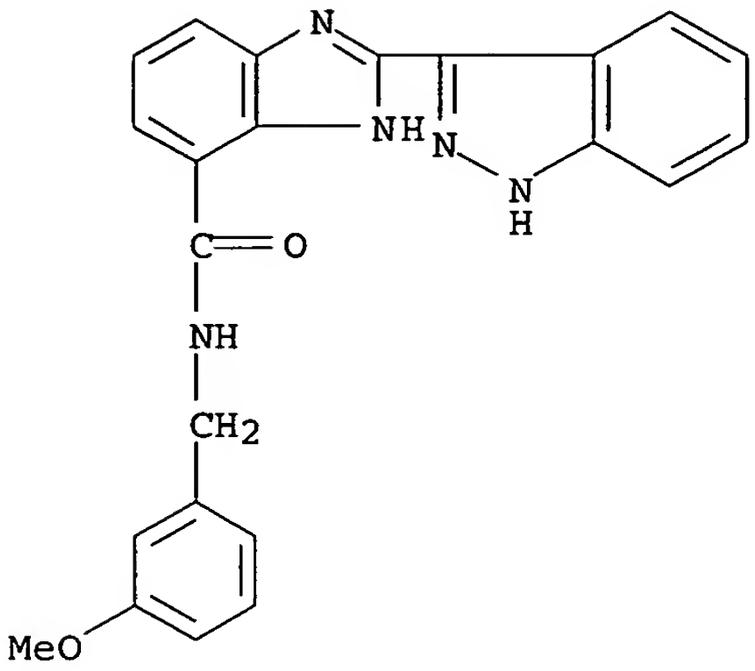
RN 518355-88-9 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, 2-(1H-indazol-3-yl)-N-(3-pyridinylmethyl)- (9CI) (CA INDEX NAME)



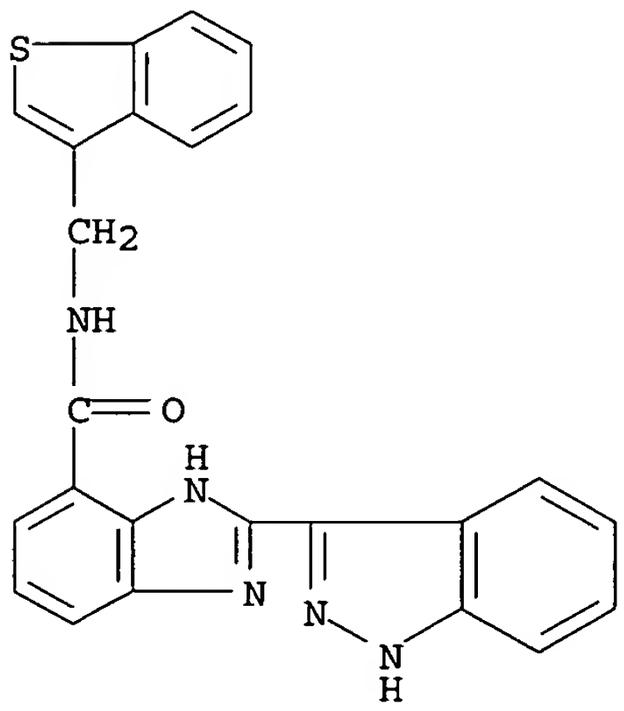
RN 518355-89-0 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(3-bromophenyl)methyl]-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



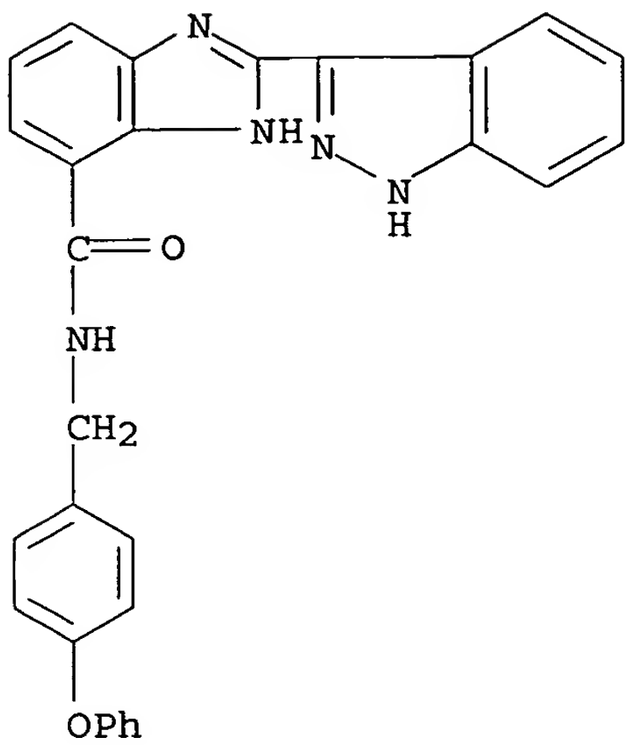
RN 518355-90-3 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, 2-(1H-indazol-3-yl)-N-[(3-methoxyphenyl)methyl]- (9CI) (CA INDEX NAME)



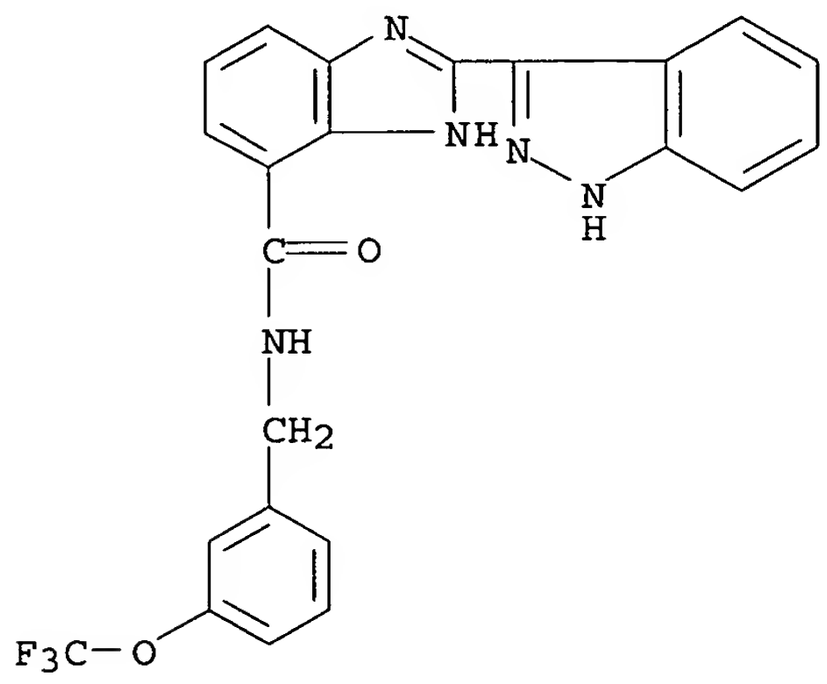
RN 518355-91-4 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-(benzo[b]thien-3-ylmethyl)-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



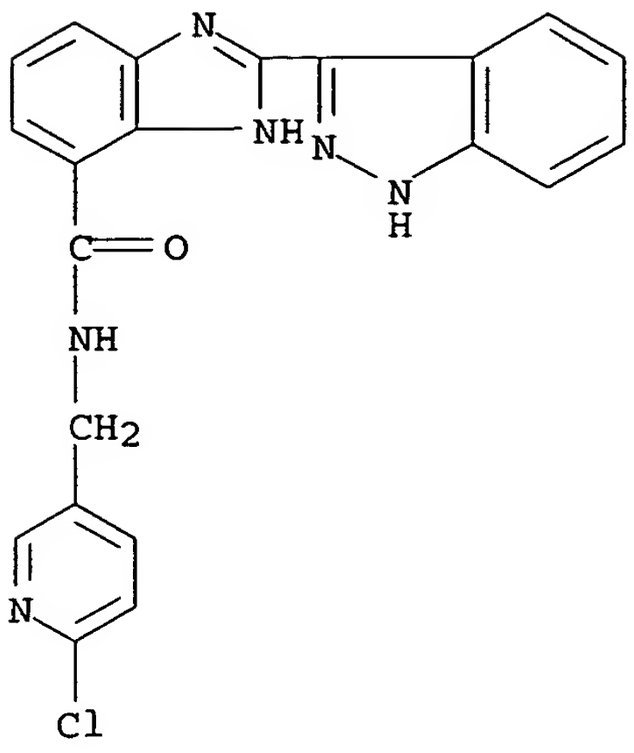
RN 518355-92-5 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, 2-(1H-indazol-3-yl)-N-[(4-phenoxyphenyl)methyl]- (9CI) (CA INDEX NAME)



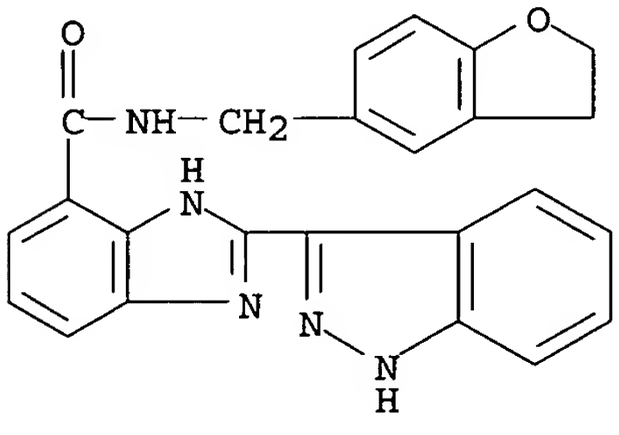
RN 518355-93-6 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, 2-(1H-indazol-3-yl)-N-[[3-(trifluoromethoxy)phenyl]methyl]- (9CI) (CA INDEX NAME)



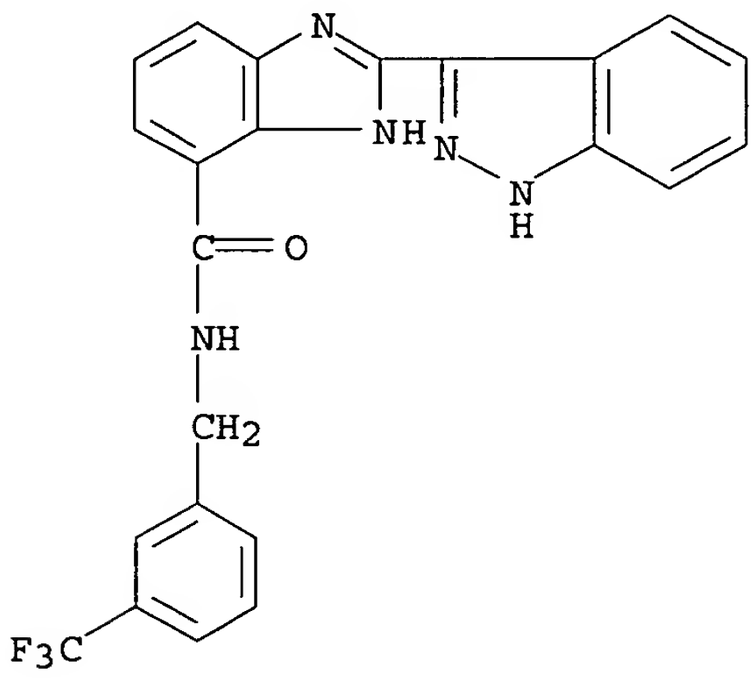
RN 518355-94-7 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(6-chloro-3-pyridinyl)methyl]-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



RN 518355-95-8 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(2,3-dihydro-5-benzofuranyl)methyl]-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)

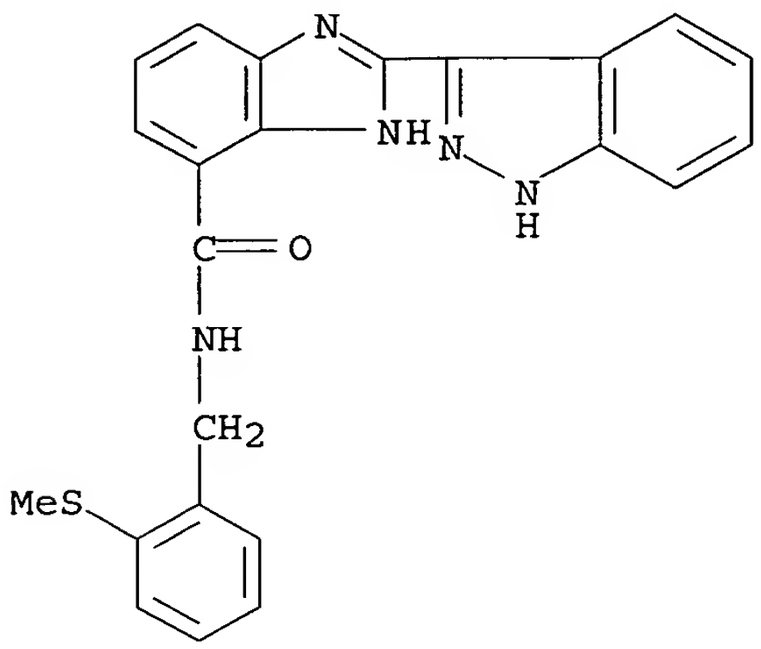


RN 518355-96-9 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, 2-(1H-indazol-3-yl)-N-[[3-(trifluoromethyl)phenyl]methyl]- (9CI) (CA INDEX NAME)

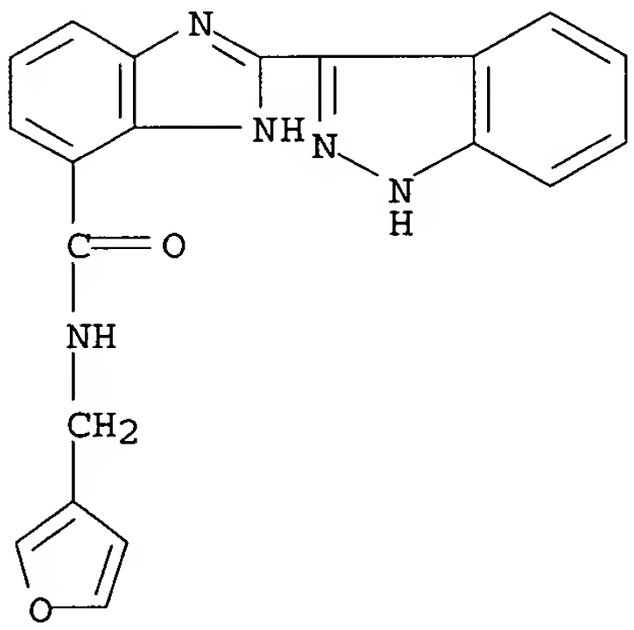


RN 518355-97-0 HCAPLUS

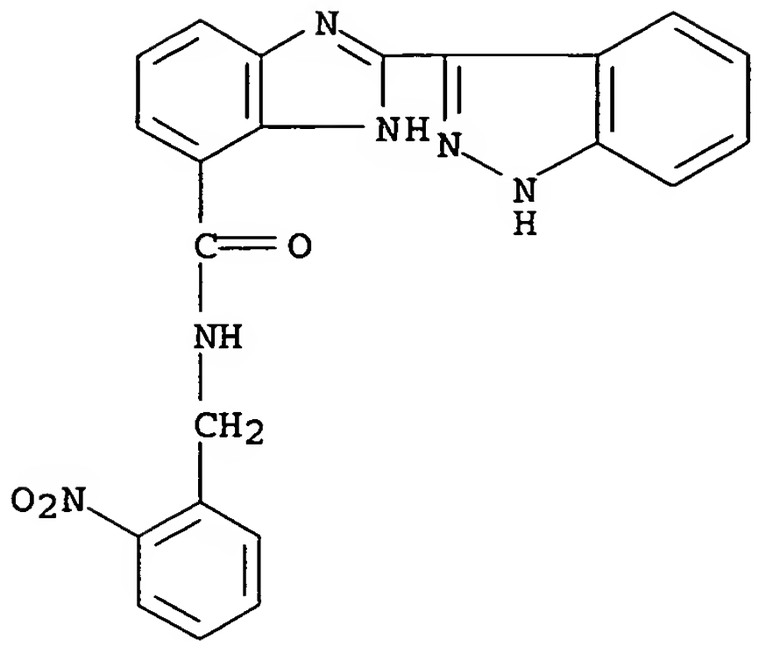
CN 1H-Benzimidazole-4-carboxamide, 2-(1H-indazol-3-yl)-N-[[2-(methylthio)phenyl]methyl]- (9CI) (CA INDEX NAME)



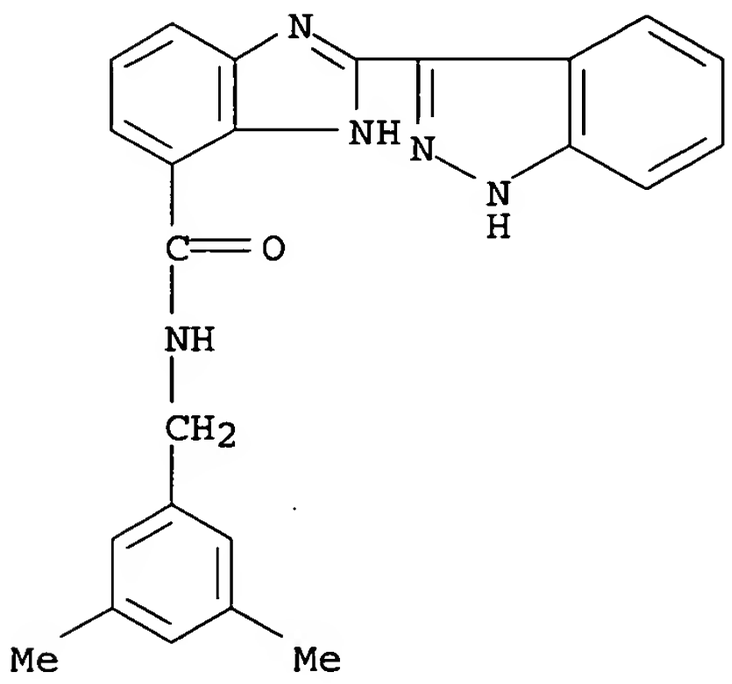
RN 518355-98-1 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-(3-furanylmethyl)-2-(1H-indazol-3-yl)-(9CI) (CA INDEX NAME)



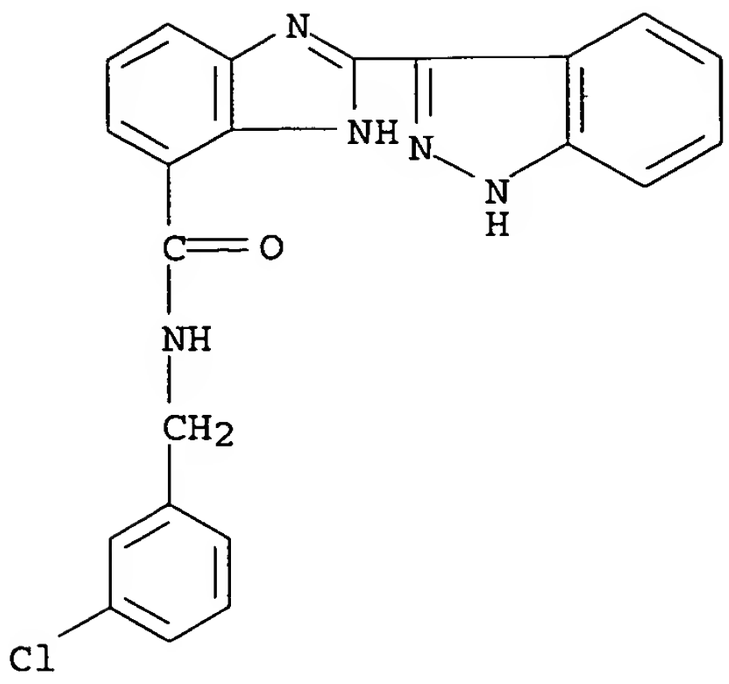
RN 518355-99-2 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, 2-(1H-indazol-3-yl)-N-[(2-nitrophenyl)methyl]- (9CI) (CA INDEX NAME)



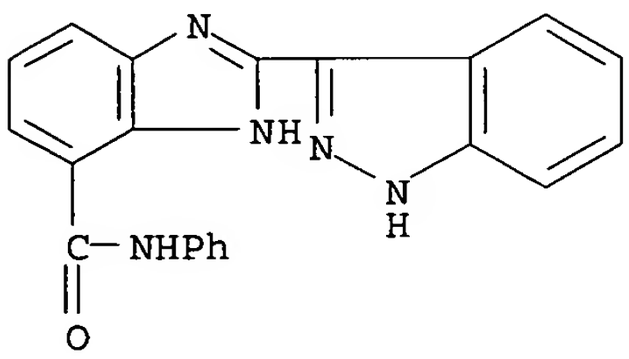
RN 518356-00-8 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(3,5-dimethylphenyl)methyl]-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



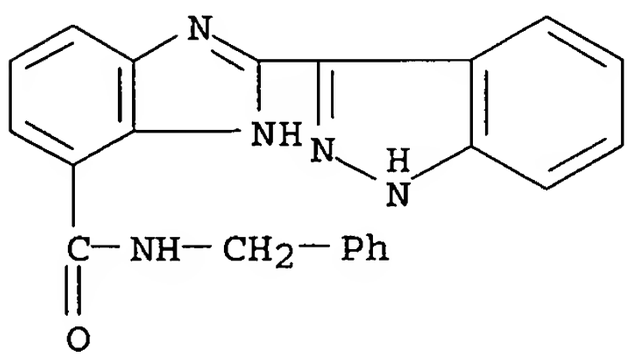
RN 518356-01-9 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(3-chlorophenyl)methyl]-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



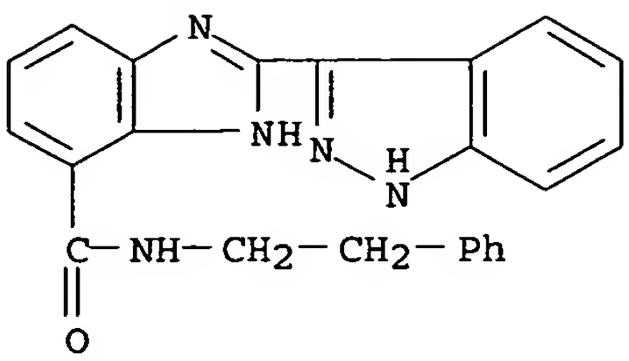
RN 518356-02-0 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, 2-(1H-indazol-3-yl)-N-phenyl- (9CI) (CA INDEX NAME)



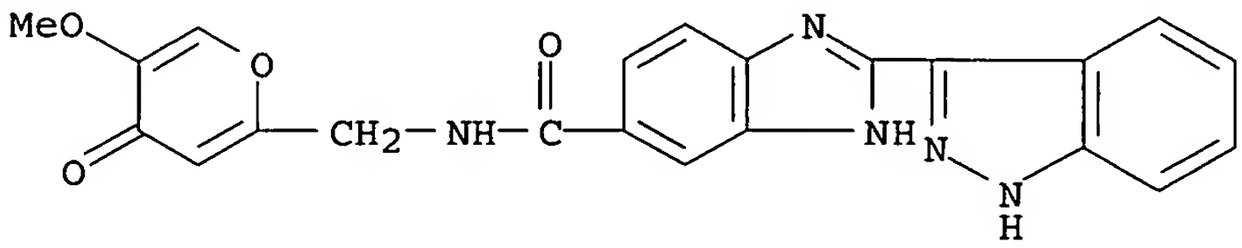
RN 518356-03-1 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, 2-(1H-indazol-3-yl)-N-(phenylmethyl)- (9CI) (CA INDEX NAME)



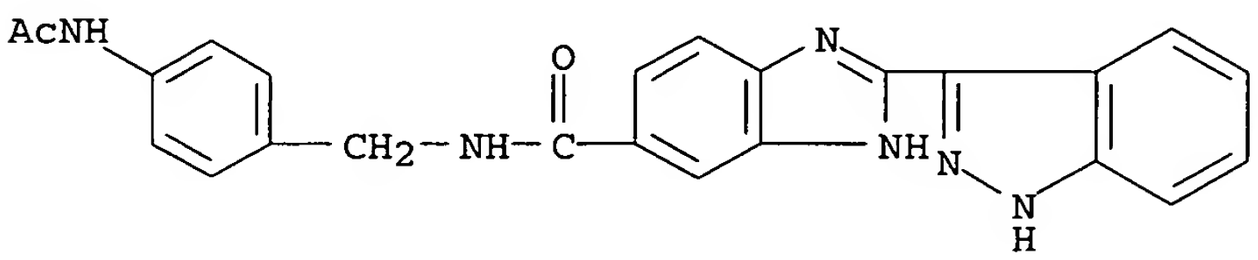
RN 518356-04-2 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, 2-(1H-indazol-3-yl)-N-(2-phenylethyl)- (9CI) (CA INDEX NAME)



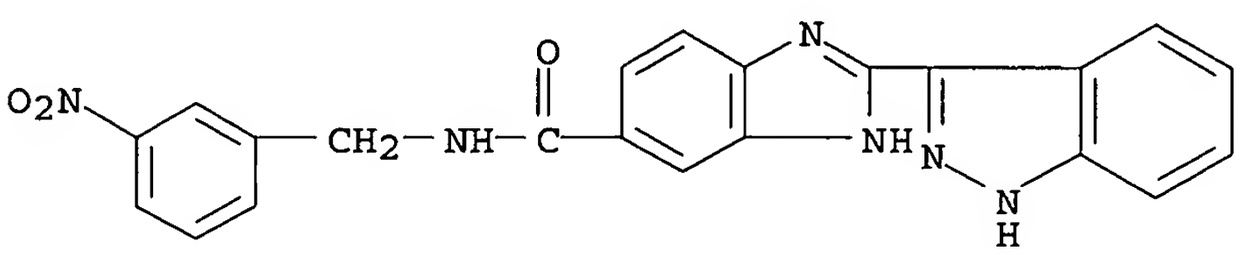
RN 518356-53-1 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, 2-(1H-indazol-3-yl)-N-[(5-methoxy-4-oxo-4H-pyran-2-yl)methyl]- (9CI) (CA INDEX NAME)



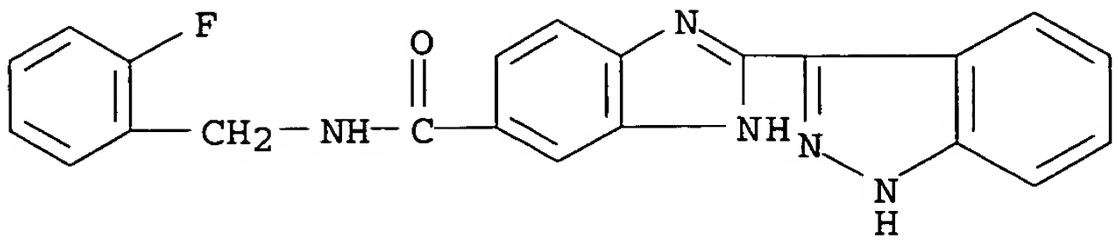
RN 518356-54-2 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[[4-(acetylamino)phenyl]methyl]-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



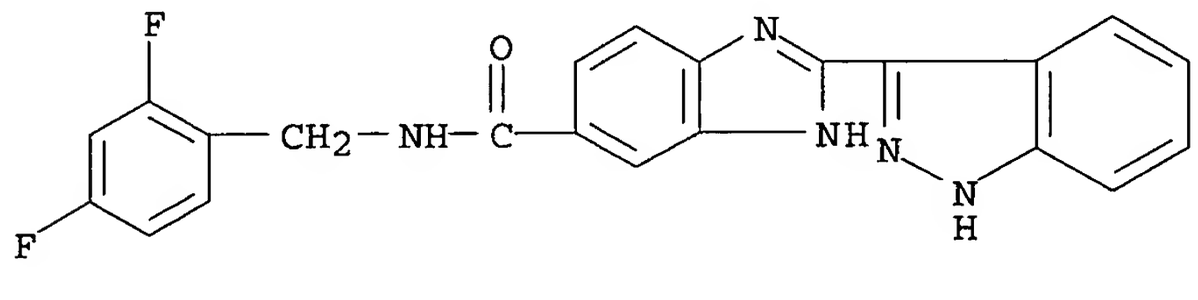
RN 518356-55-3 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, 2-(1H-indazol-3-yl)-N-[(3-nitrophenyl)methyl]- (9CI) (CA INDEX NAME)



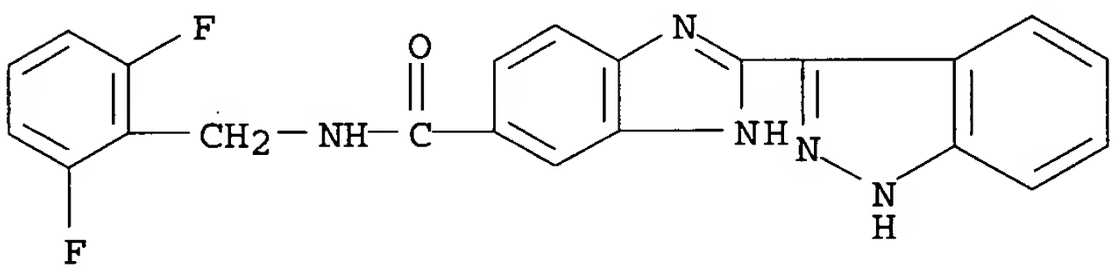
RN 518356-56-4 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(2-fluorophenyl)methyl]-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



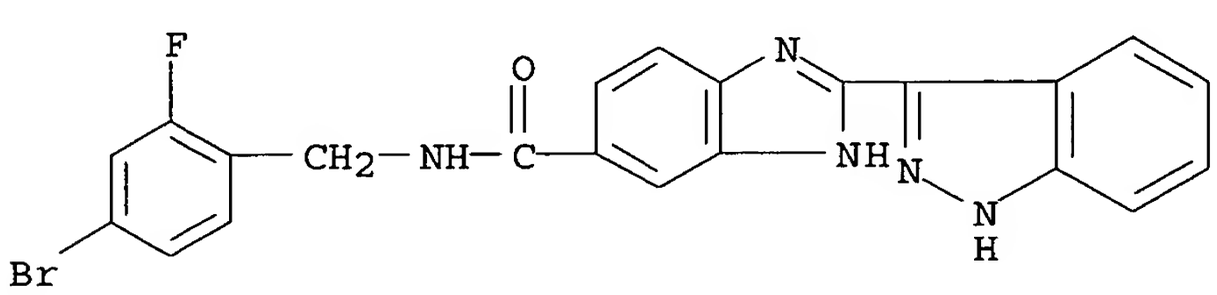
RN 518356-57-5 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(2,4-difluorophenyl)methyl]-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



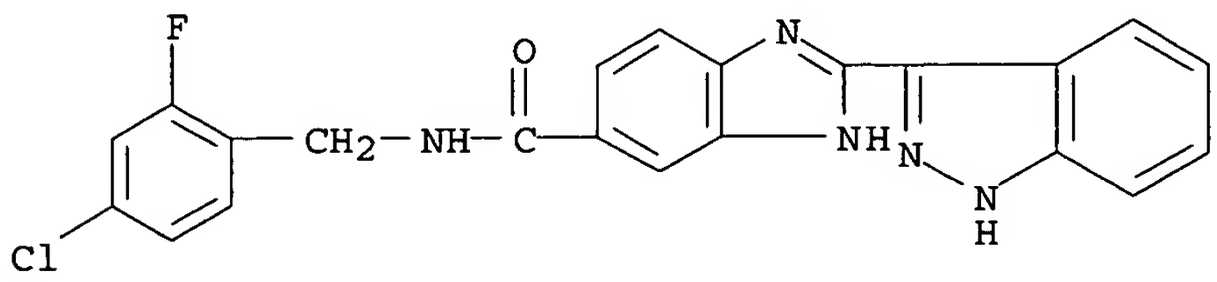
RN 518356-58-6 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(2,6-difluorophenyl)methyl]-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



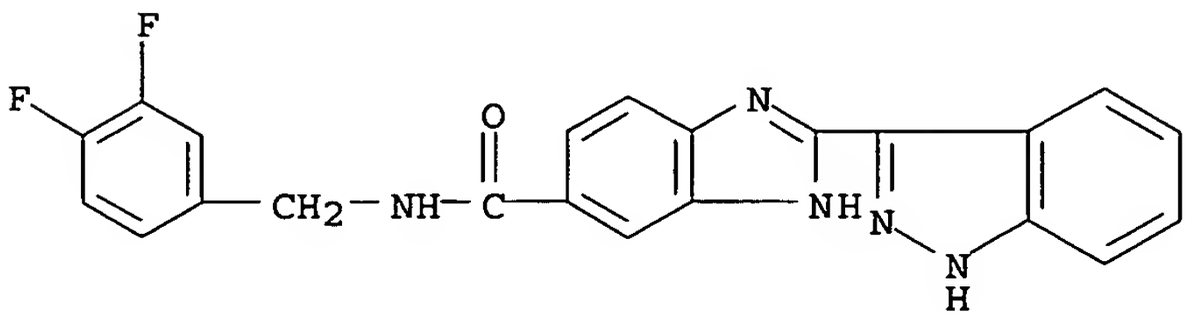
RN 518356-59-7 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(4-bromo-2-fluorophenyl)methyl]-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



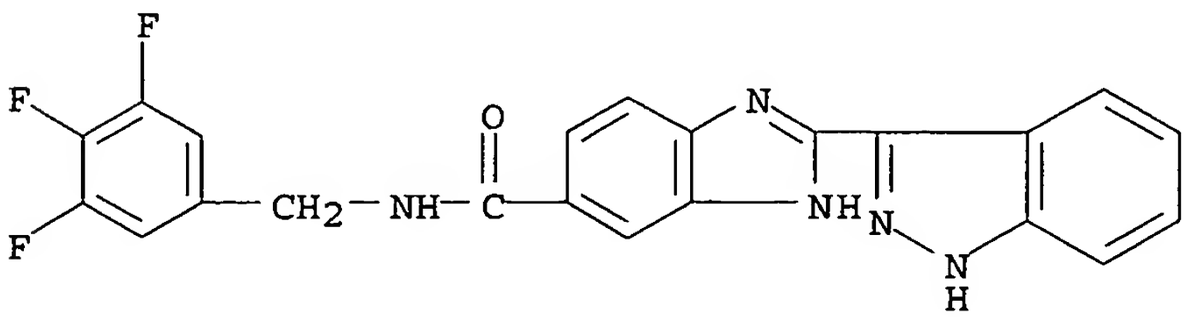
RN 518356-60-0 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(4-chloro-2-fluorophenyl)methyl]-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



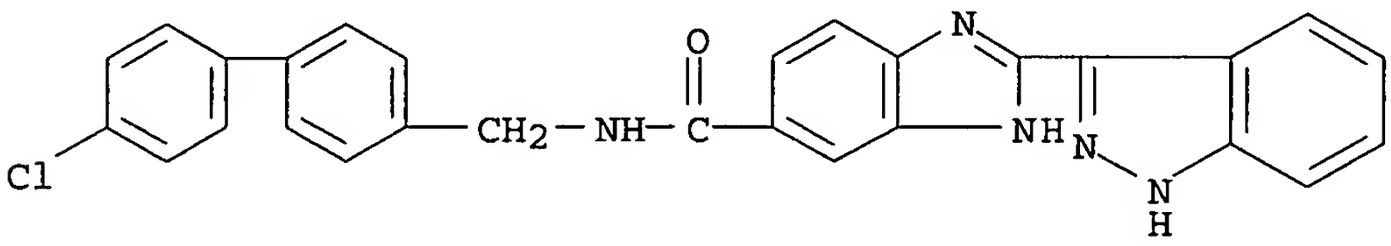
RN 518356-61-1 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(3,4-difluorophenyl)methyl]-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



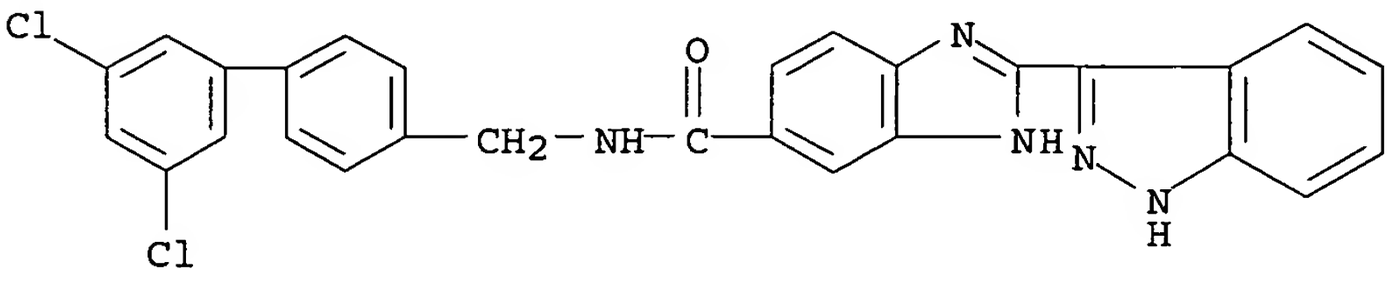
RN 518356-62-2 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, 2-(1H-indazol-3-yl)-N-[(3,4,5-trifluorophenyl)methyl]- (9CI) (CA INDEX NAME)



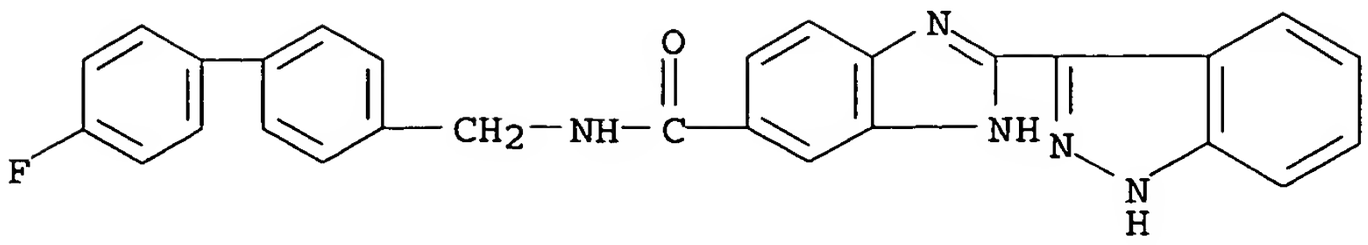
RN 518356-63-3 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(4'-chloro[1,1'-biphenyl]-4-yl)methyl]-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



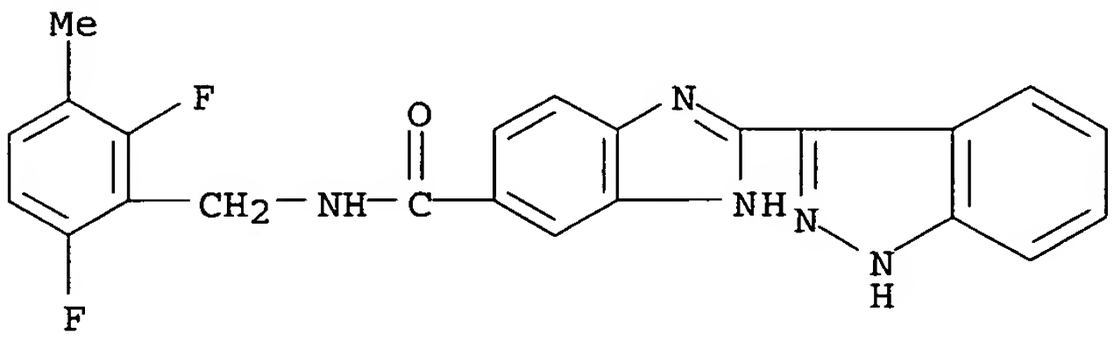
RN 518356-64-4 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(3',5'-dichloro[1,1'-biphenyl]-4-yl)methyl]-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



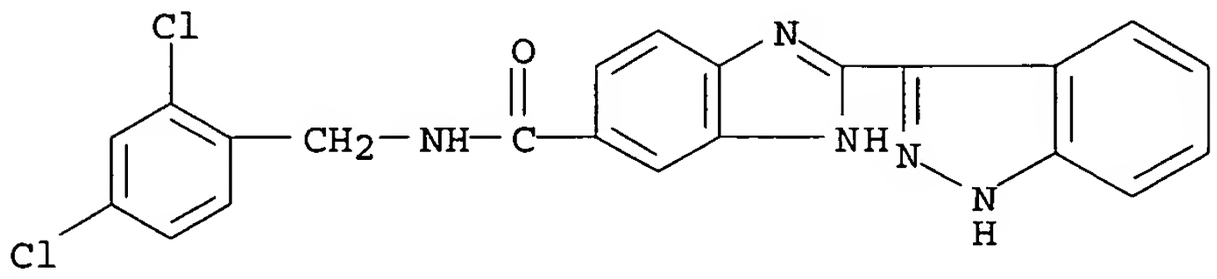
RN 518356-65-5 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(4'-fluoro[1,1'-biphenyl]-4-yl)methyl]-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



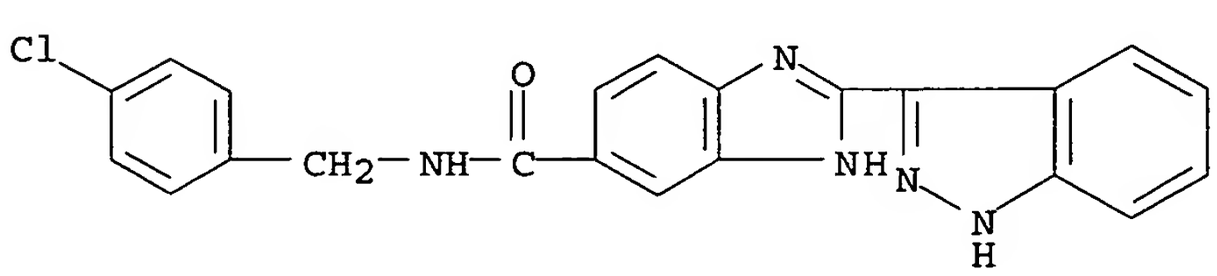
RN 518356-66-6 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(2,6-difluoro-3-methylphenyl)methyl]-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



RN 518356-67-7 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(2,4-dichlorophenyl)methyl]-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



RN 518356-68-8 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(4-chlorophenyl)methyl]-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



RN 518356-69-9 HCAPLUS
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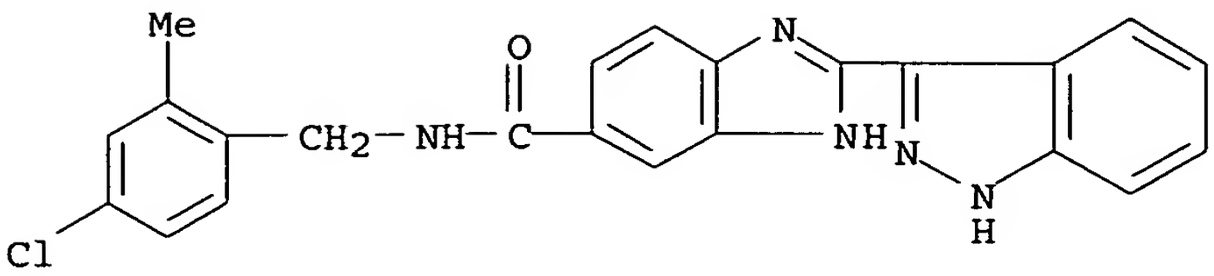
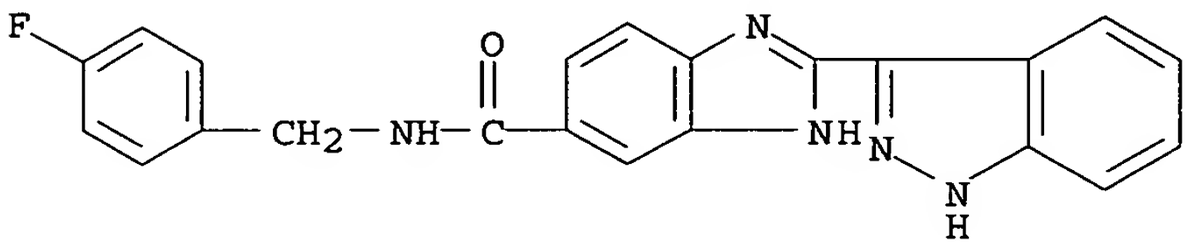
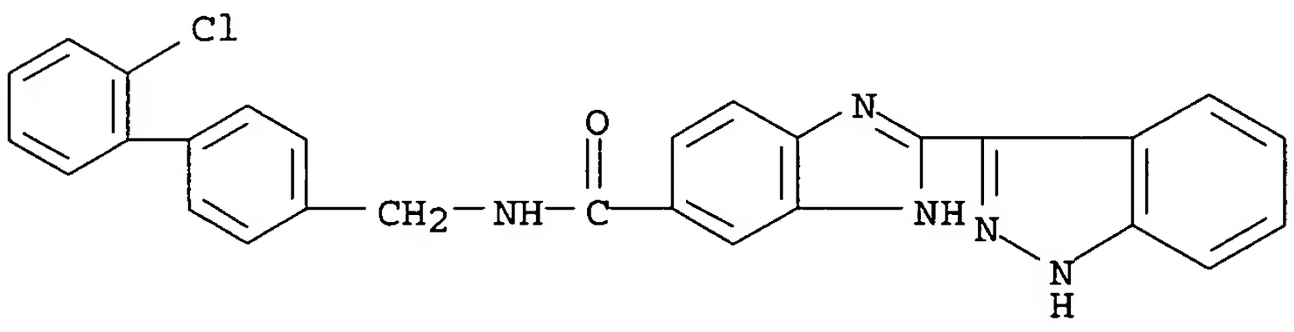


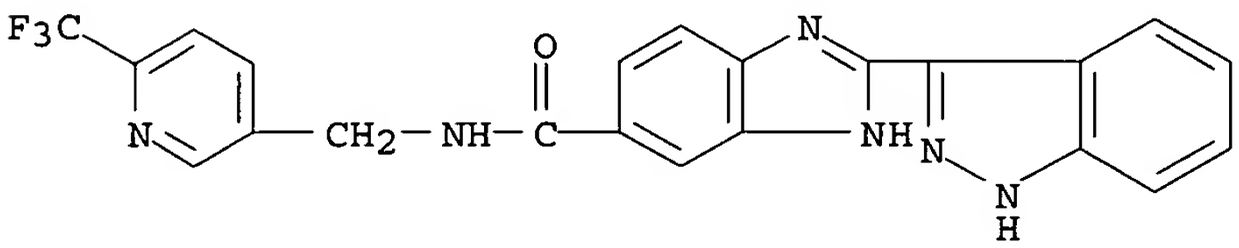
RN 518356-70-2 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(4-fluorophenyl)methyl]-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



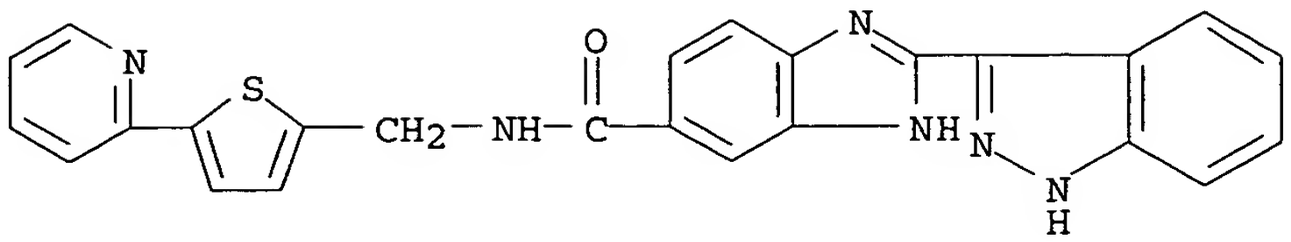
RN 518356-71-3 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(2'-chloro[1,1'-biphenyl]-4-yl)methyl]-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



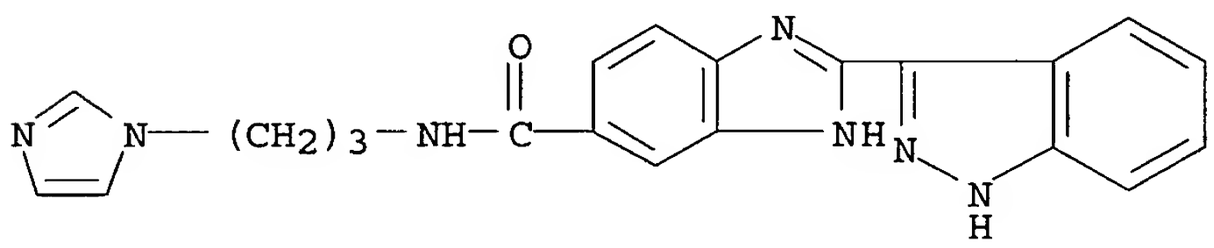
RN 518356-72-4 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, 2-(1H-indazol-3-yl)-N-[[6-(trifluoromethyl)-3-pyridinyl]methyl]- (9CI) (CA INDEX NAME)



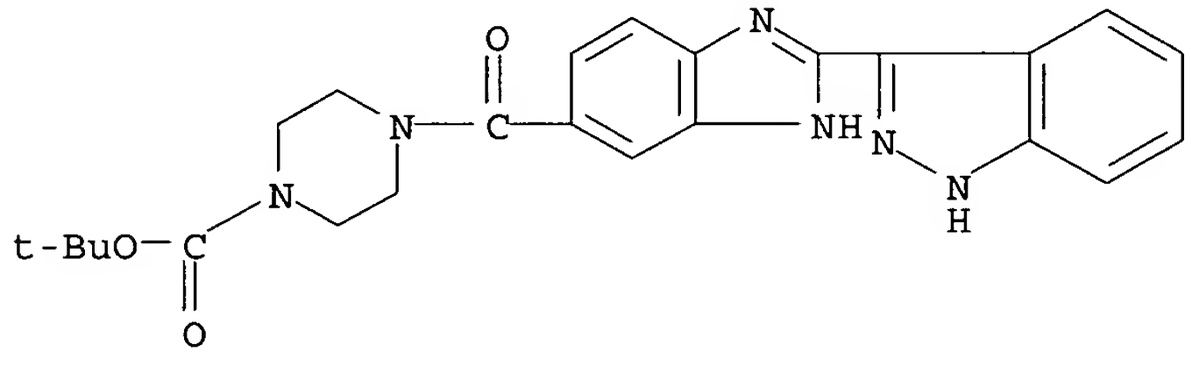
RN 518356-73-5 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, 2-(1H-indazol-3-yl)-N-[[5-(2-pyridinyl)-2-thienyl]methyl]- (9CI) (CA INDEX NAME)



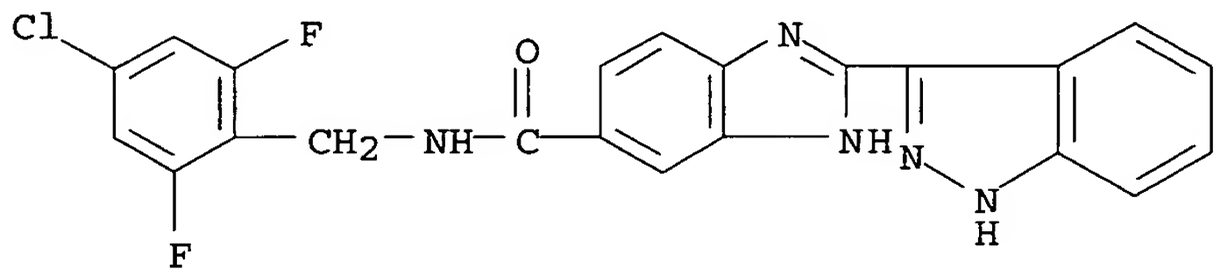
RN 518356-74-6 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[3-(1H-imidazol-1-yl)propyl]-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



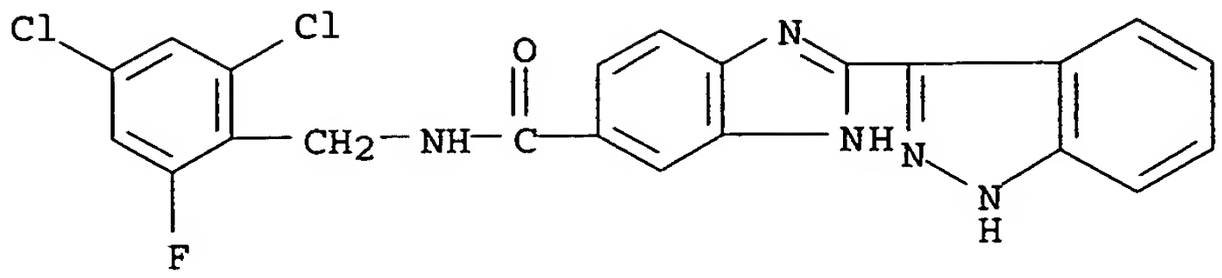
RN 518356-75-7 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-[[2-(1H-indazol-3-yl)-1H-benzimidazol-5-yl]carbonyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



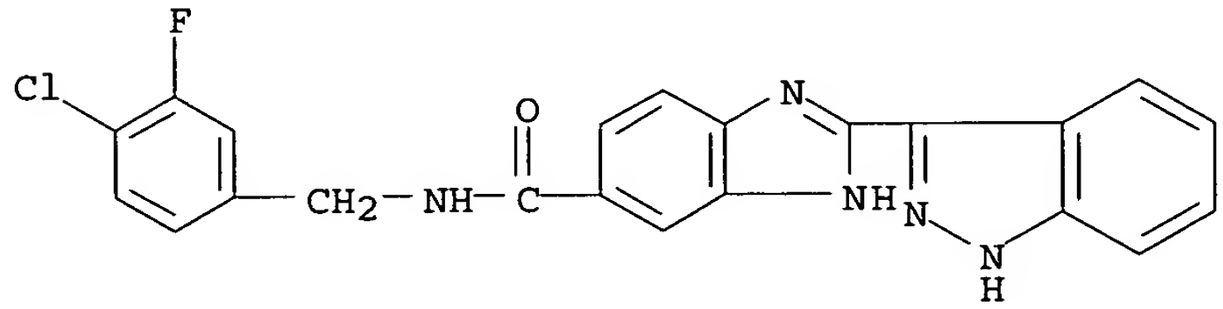
RN 518356-76-8 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(4-chloro-2,6-difluorophenyl)methyl]-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



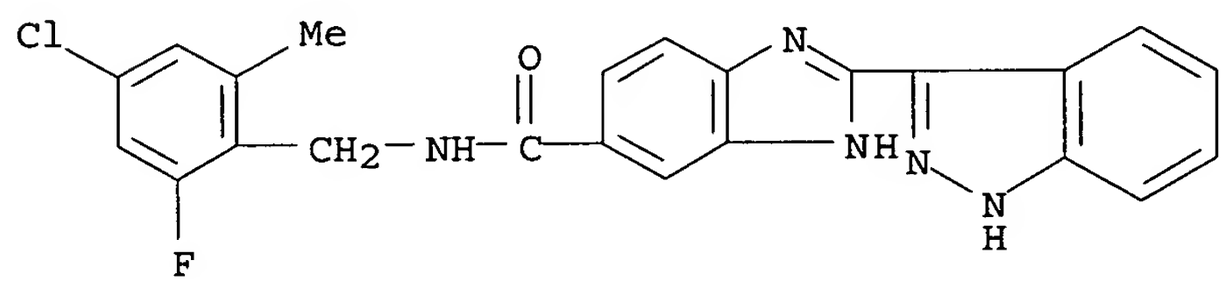
RN 518356-77-9 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(2,4-dichloro-6-fluorophenyl)methyl]-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



RN 518356-78-0 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(4-chloro-3-fluorophenyl)methyl]-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



RN 518356-79-1 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(4-chloro-2-fluoro-6-methylphenyl)methyl]-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



RN 518356-80-4 HCAPLUS
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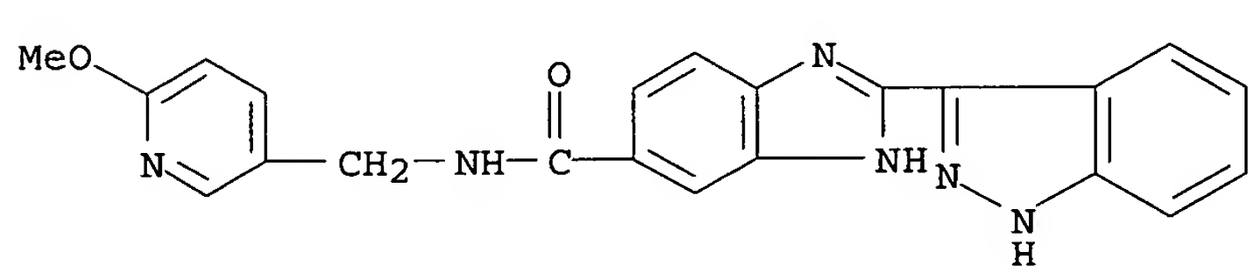

RN 518987-99-0 HCAPLUS
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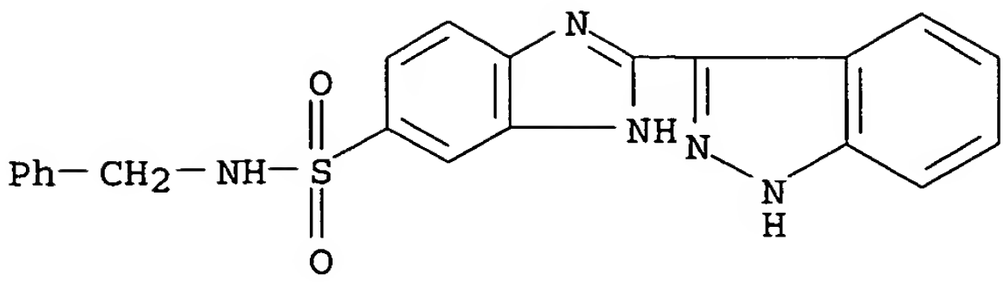
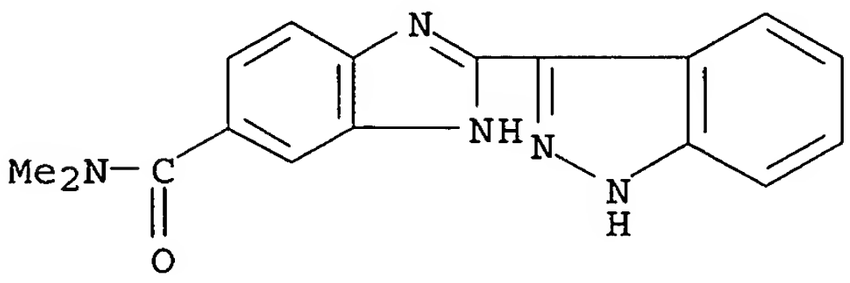
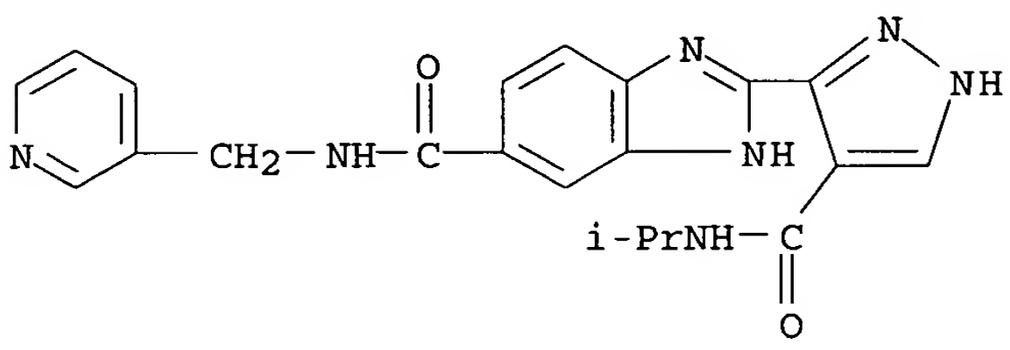


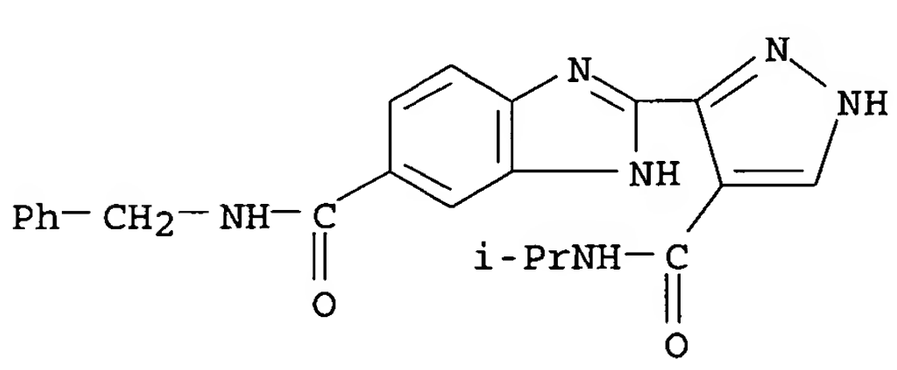
RN 518988-03-9 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, 2-(1H-indazol-3-yl)-N,N-dimethyl- (9CI) (CA INDEX NAME)



RN 518988-07-3 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, 2-[4-[[(1-methylethyl)amino]carbonyl]-1H-pyrazol-3-yl]-N-(3-pyridinylmethyl)- (9CI) (CA INDEX NAME)



RN 518988-11-9 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, 2-[4-[[(1-methylethyl)amino]carbonyl]-1H-pyrazol-3-yl]-N-(phenylmethyl)- (9CI) (CA INDEX NAME)



RN 518988-12-0 HCAPLUS
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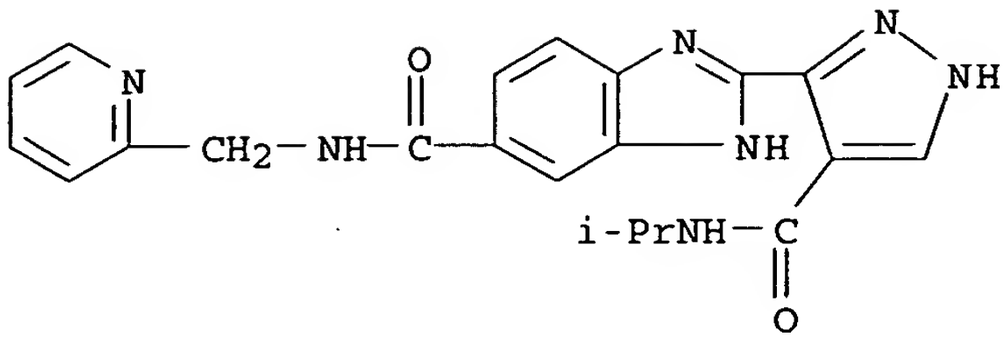

RN 518988-13-1 HCAPLUS
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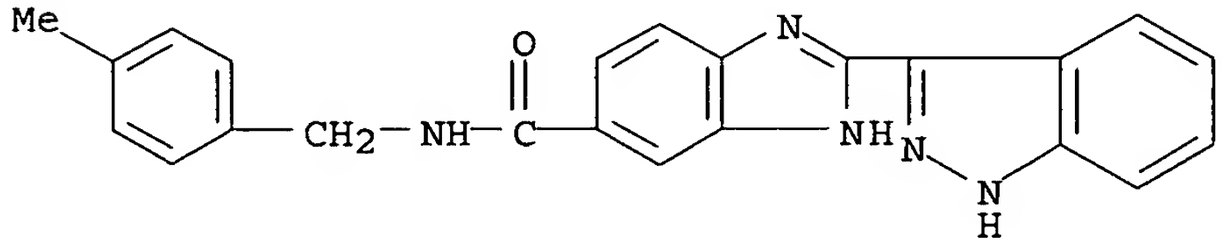

RN 518988-14-2 HCAPLUS
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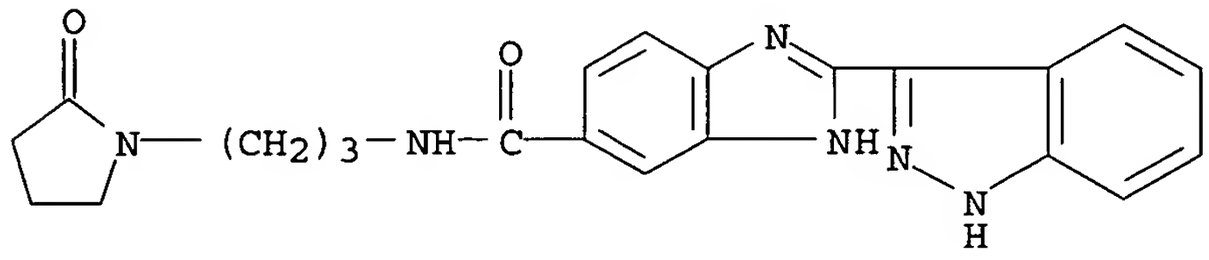
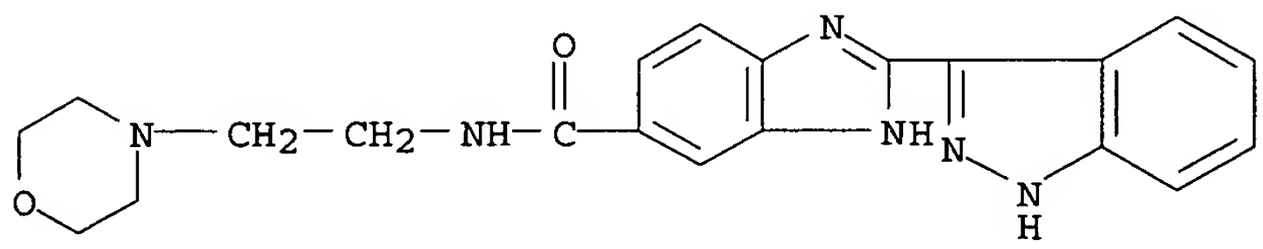
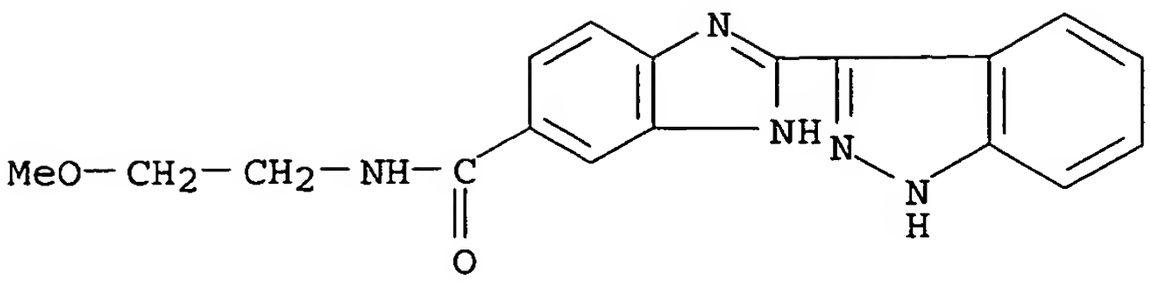


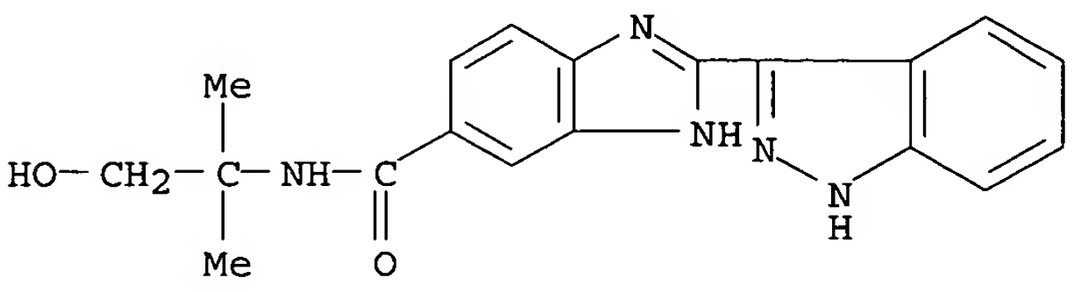
RN 518988-15-3 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, 2-(1H-indazol-3-yl)-N-[2-(4-morpholinyl)ethyl]- (9CI) (CA INDEX NAME)



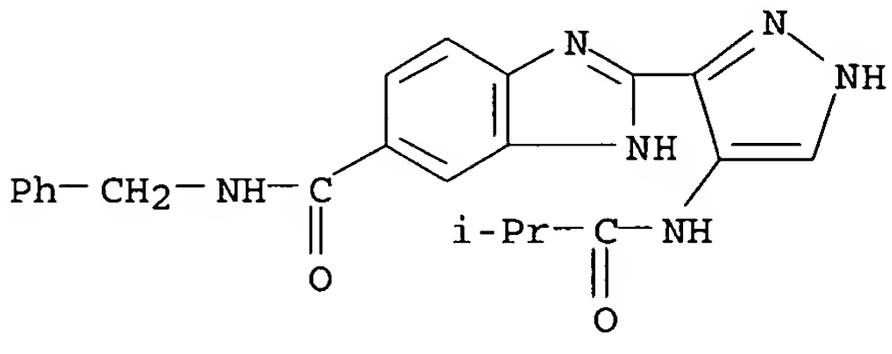
RN 518988-17-5 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, 2-(1H-indazol-3-yl)-N-(2-methoxyethyl)- (9CI) (CA INDEX NAME)



RN 518988-19-7 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-(2-hydroxy-1,1-dimethylethyl)-2-(1H-indazol-3-yl)- (9CI) (CA INDEX NAME)



RN 518988-25-5 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, 2-[4-[(2-methyl-1-oxopropyl)amino]-1H-pyrazol-3-yl]-N-(phenylmethyl)- (9CI) (CA INDEX NAME)



RN 518988-27-7 HCAPLUS
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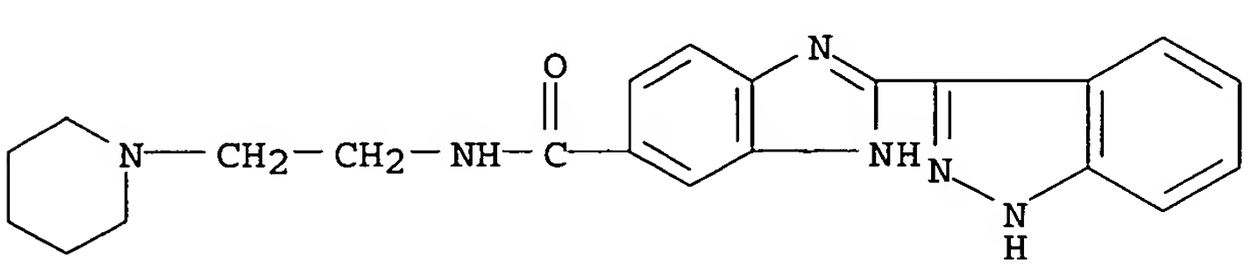

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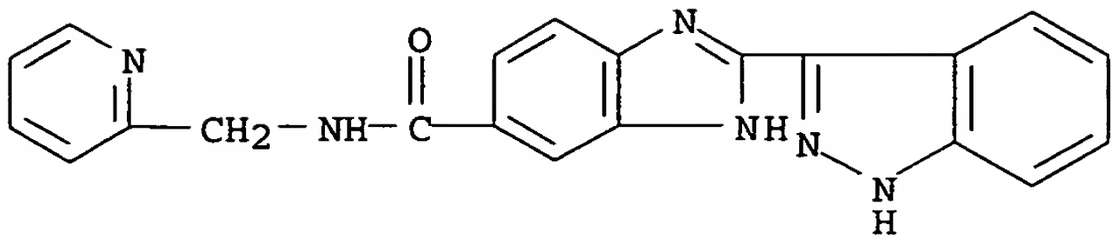

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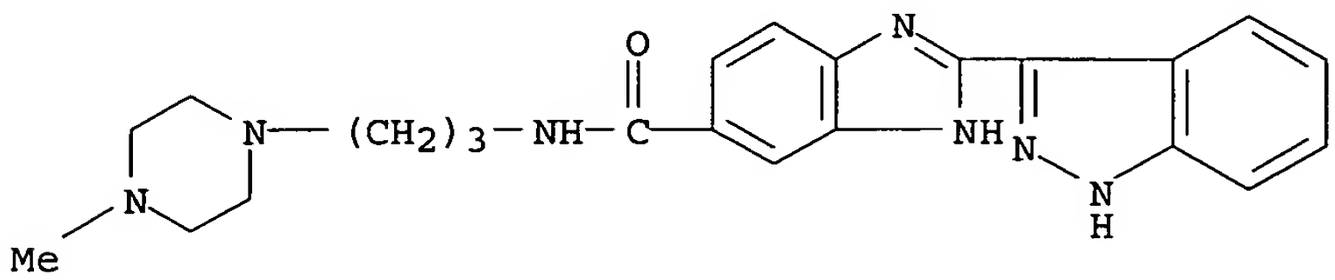

RN 518989-46-3 HCAPLUS
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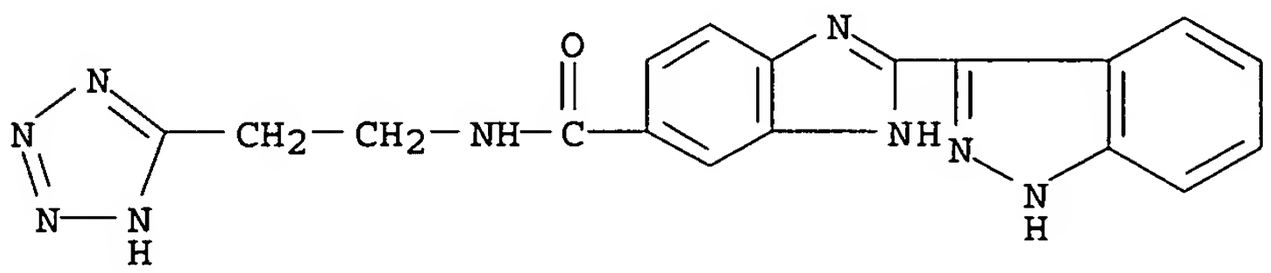

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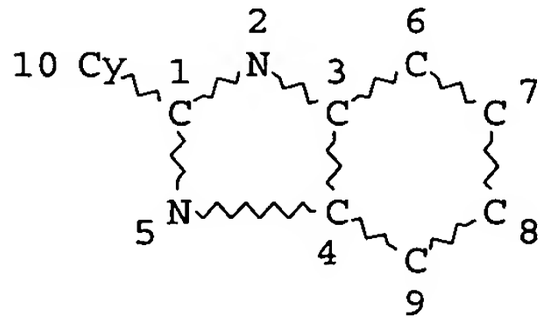

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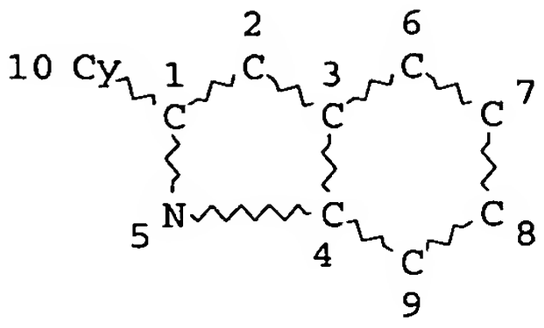

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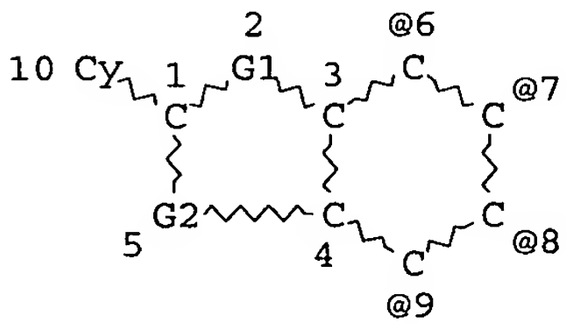

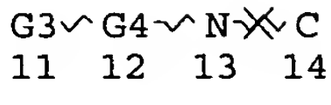

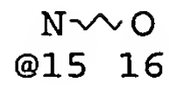

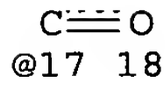

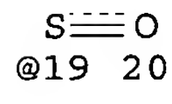

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L13 7274 SEA FILE=HCAPLUS ABB=ON PLU=ON ?KAPPA?(L)KINASE
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L15 3 SEA FILE=HCAPLUS ABB=ON PLU=ON L14 NOT L7
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L22 6 SEA FILE=HCAPLUS ABB=ON PLU=ON L6 AND L21
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L24 ANSWER 1 OF 4 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:701969 HCAPLUS
DOCUMENT NUMBER: 141:207209
TITLE: Preparation of substituted imidazoles as protein tyrosine phosphatase inhibitors for treatment of diabetes and other PTPase mediated conditions
INVENTOR(S): Mjalli, Adnan M. M.; Andrews, Robert C.; Yarragunta, Ravindra R.; Xie, Rongyuan; Subramanian, Govindan; Quada, James C., Jr.; Arimilli, Murty N.; Polisetti, Dharma R.
PATENT ASSIGNEE(S): Transtech Pharma Inc., USA
SOURCE: PCT Int. Appl., 281 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004071447	A2	20040826	WO 2004-US4074	20040212
WO 2004071447	A3	20041223		
WO 2004071447	B1	20050310		
WO 2004071447	C2	20051013		
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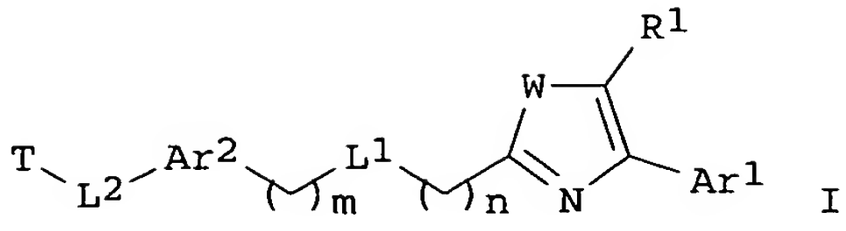
CA 2514363	AA	20040826	CA 2004-2514363	20040212
US 2004192743	A1	20040930	US 2004-777488	20040212
EP 1594847	A2	20051116	EP 2004-710607	20040212
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				

PRIORITY APPLN. INFO.: US 2003-446977P P 20030212
WO 2004-US4074 W 20040212
OTHER SOURCE(S): MARPAT 141:207209
GI



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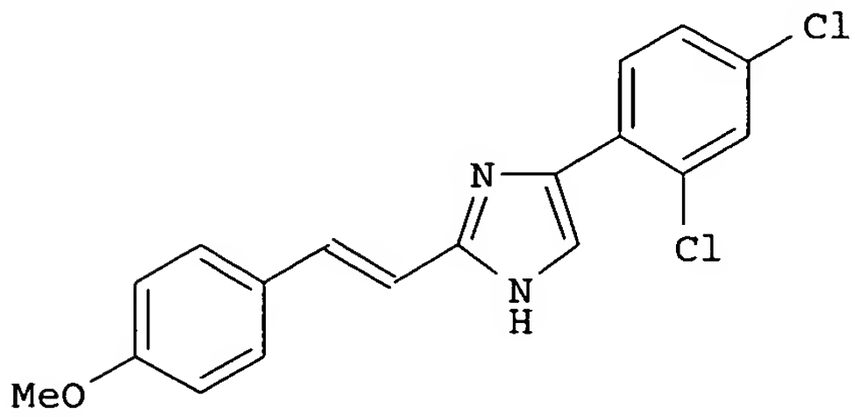


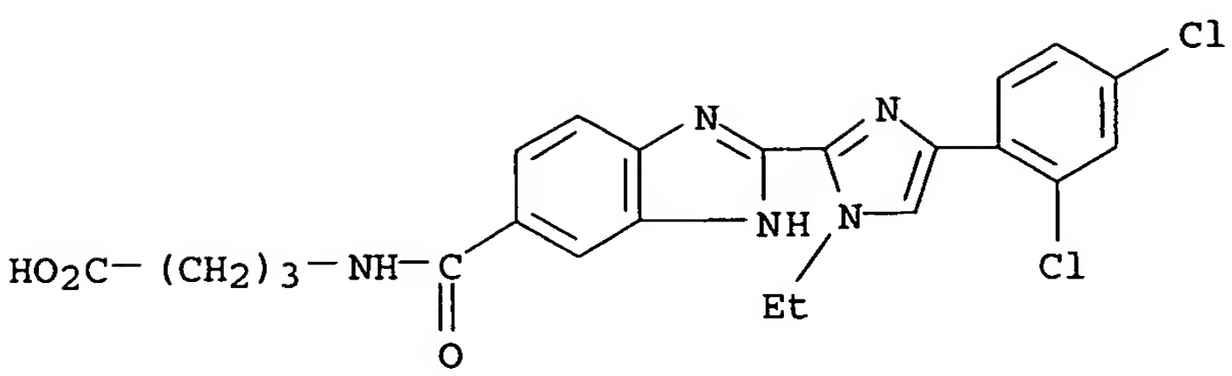
II

AB Title imidazoles and analogs I [wherein m, n = independently 0-2; W = O, S, NR2; R1 = H, halo, CN, alkyl, (hetero)aryl, heterocyclyl, etc.; R2 = H, alkyl, (hetero)aryl(alkyl), heterocyclyl(alkyl), etc.; Ar1 = (un)substituted optionally fused (hetero)aryl; Ar2 = (un)substituted optionally fused (hetero)arylene; L1 = a bond, (un)substituted ethylene, NHCO, NH, NHSO2, etc.; L2 = CH2, O, alkylene, (hetero)arylene, etc.; T = H, (un)substituted (cyclo)alkyl, heterocyclyl, (hetero)aryl, etc.; and pharmaceutically acceptable slats, solvates, and prodrugs thereof] were prepared as inhibitors of protein tyrosine phosphatases (PTPases). For example, reaction of trans-4-methoxycinnamic acid with 2,4-dichlorophenacyl bromide in the presence of DIEA in DMF gave the keto-ester (no data), which was treated with ammonium acetate in glacial AcOH to afford (E)-II (56%). Compds. of the invention inhibited PTP 1B activity with IC50 values ranging from about 0.01 μM to about 20 μM. Thus, I and pharmaceutical compns. comprising them may be useful for the management, treatment, control, and adjunct treatment of diseases mediated by PTPase activity, such as Type I diabetes, Type II diabetes, immune dysfunction, AIDS, autoimmune diseases, glucose intolerance, obesity, cancer, psoriasis, allergic diseases, infectious diseases, inflammatory diseases, diseases involving the modulated synthesis and/or production of growth hormone or cytokines, of Alzheimer's disease (no data).

IT **744242-02-2P**, 4-[[[2-[4-(2,4-Dichlorophenyl)-1-ethyl-1H-imidazol-2-yl]-3H-benzimidazol-5-yl]carbonyl]amino]butyric acid
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(PTPase inhibitor; preparation of substituted imidazoles as PTPase inhibitors for treatment of diabetes and other PTPase mediated conditions)

RN 744242-02-2 HCAPLUS

CN Butanoic acid, 4-[[[2-[4-(2,4-dichlorophenyl)-1-ethyl-1H-imidazol-2-yl]-1H-benzimidazol-5-yl]carbonyl]amino]- (9CI) (CA INDEX NAME)



L24 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:319887 HCAPLUS
DOCUMENT NUMBER: 134:326769
TITLE: Preparation of amino acid indolecarboxamides as modulators of NFκB activity.
INVENTOR(S): Ritzeler, Olaf; Stilz, Hans Ulrich; Neises, Bernhard; Jaehne, Gerhard; Habermann, Joerg
PATENT ASSIGNEE(S): Aventis Pharma Deutschland G.m.b.H., Germany
SOURCE: PCT Int. Appl., 52 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001030774	A1	20010503	WO 2000-EP10210	20001017
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
DE 19951360	A1	20010503	DE 1999-19951360	19991026
CA 2389165	AA	20010503	CA 2000-2389165	20001017
BR 2000015026	A	20020716	BR 2000-15026	20001017
EP 1261601	A1	20021204	EP 2000-974405	20001017
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TR 200201144	T2	20030221	TR 2002-200201144	20001017
EE 200200217	A	20030616	EE 2002-217	20001017
JP 2003519101	T2	20030617	JP 2001-533128	20001017
NZ 518587	A	20040625	NZ 2000-518587	20001017
AU 781553	B2	20050526	AU 2001-12728	20001017
RU 2255087	C2	20050627	RU 2002-113651	20001017
NO 2002001808	A	20020417	NO 2002-1808	20020417
ZA 2002003204	A	20021023	ZA 2002-3204	20020423
US 2003119820	A1	20030626	US 2002-263691	20021004
HK 1049671	A1	20050401	HK 2003-101851	20030314
US 2004209868	A1	20041021	US 2004-842427	20040511
PRIORITY APPLN. INFO.:			DE 1999-19951360	A 19991026
			WO 2000-EP10210	W 20001017
			US 2000-695412	B1 20001025
			US 2002-263691	A1 20021004

OTHER SOURCE(S): MARPAT 134:326769
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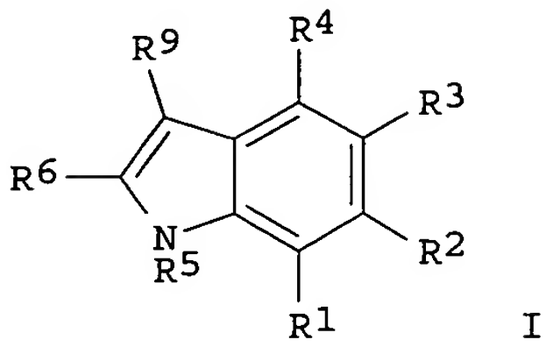


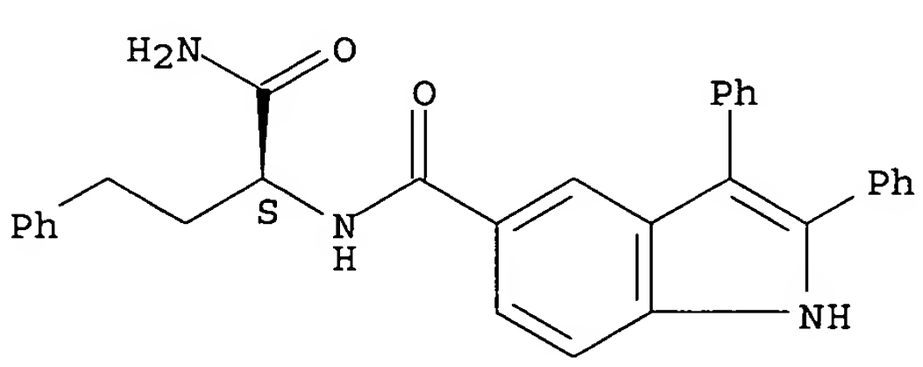
I

AB Title compds. [I; 1 of R1-R4 = DNR7CHR8Z; the remainder of R1-R4 = H, halo, (substituted) aryl, heteroaryl, heterocyclyl, alkyl, etc.; D = CO, SO, SO2; R7 = H, alkyl; R8 = R9, amino acid residue; R9 = halo, cyano, CF3, (substituted) aryl, heteroaryl, heterocyclyl, alkyl, etc.; Z = (substituted) aryl, heteroaryl, heterocyclyl, etc.; R7R8, R8Z = atoms to form a specified ring; R5 = H, OH, O; R6 = (substituted) aryl, heteroaryl, heterocyclyl], were prepared Thus, 2,3-diphenyl-1H-indol-5-carboxylic acid in DMF was treated successively with L-homophenylalaninamide hydrochloride, TOTU, and diisopropylamine followed by 6 h stirring to give 2,3-diphenyl-1H-indol-5-carboxylic acid (1-carbamoyl-3-phenylpropyl)amide. Tested I inhibited Iκ B **kinase** with IC50 = 0.050-32 μM.

IT **336857-87-5P 336857-88-6P 336857-89-7P**
336857-90-0P 336857-91-1P 336857-92-2P
336857-94-4P 336857-96-6P 336857-97-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of amino acid indolecarboxamides as modulators of NFκB activity)

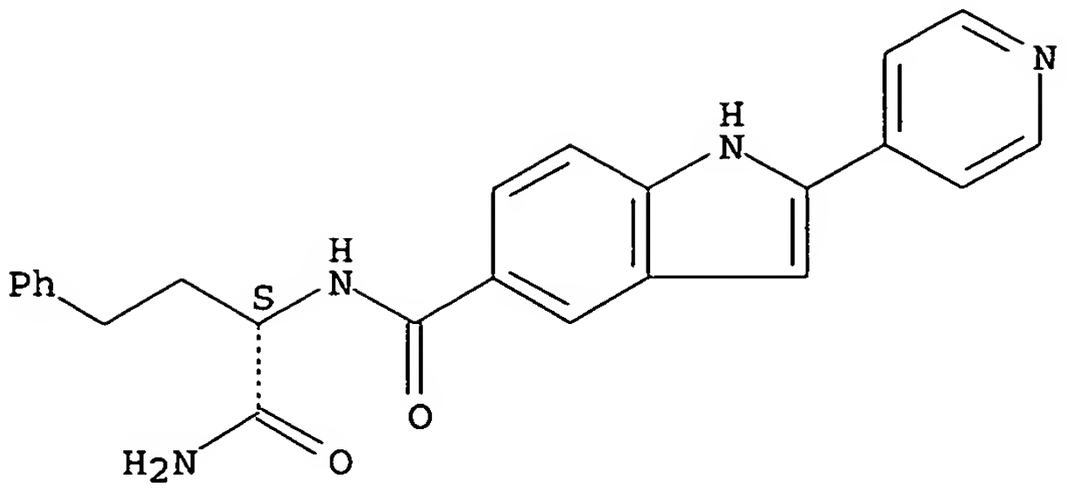
RN 336857-87-5 HCAPLUS
CN 1H-Indole-5-carboxamide, N-[(1S)-1-(aminocarbonyl)-3-phenylpropyl]-2,3-diphenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



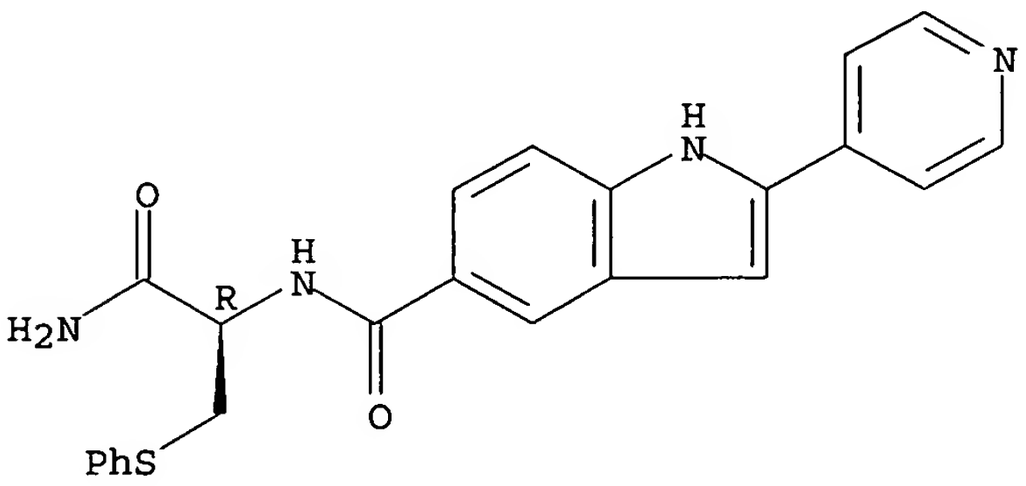
RN 336857-88-6 HCAPLUS
CN 1H-Indole-5-carboxamide, N-[(1S)-1-(aminocarbonyl)-3-phenylpropyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



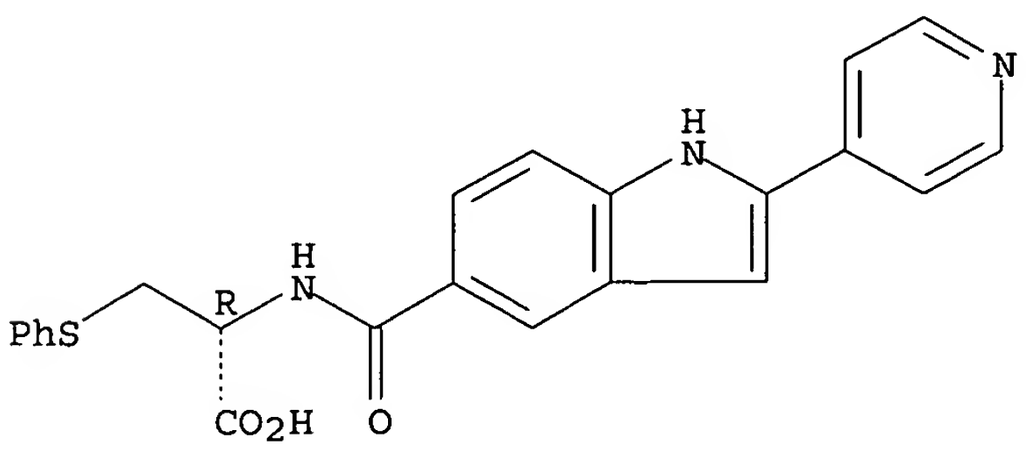
RN 336857-89-7 HCAPLUS
CN 1H-Indole-5-carboxamide, N-[(1R)-2-amino-2-oxo-1-[(phenylthio)methyl]ethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



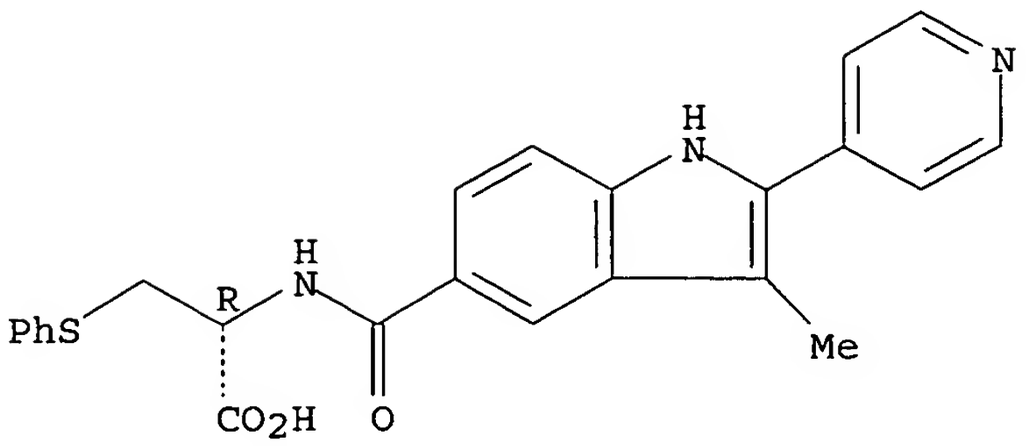
RN 336857-90-0 HCAPLUS
CN L-Cysteine, S-phenyl-N-[[2-(4-pyridinyl)-1H-indol-5-yl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



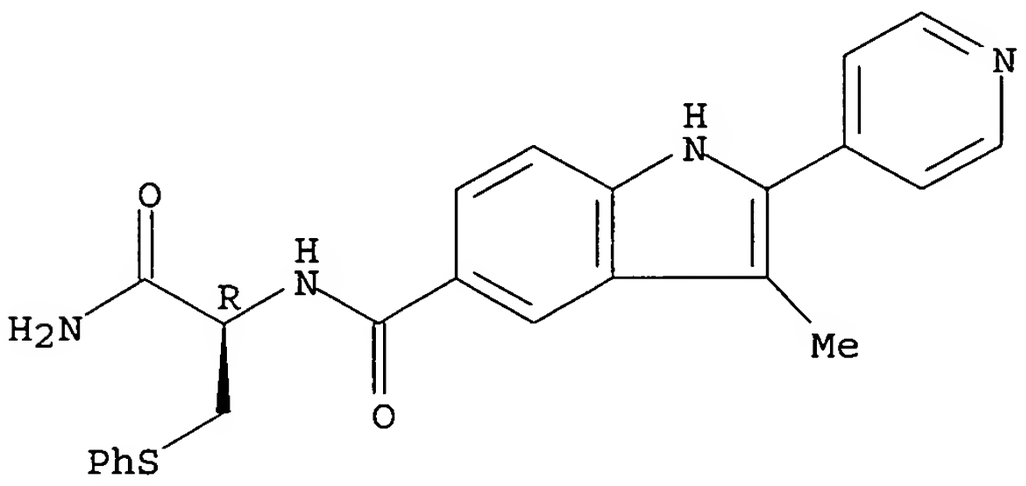
RN 336857-91-1 HCAPLUS
CN L-Cysteine, N-[[3-methyl-2-(4-pyridinyl)-1H-indol-5-yl]carbonyl]-S-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



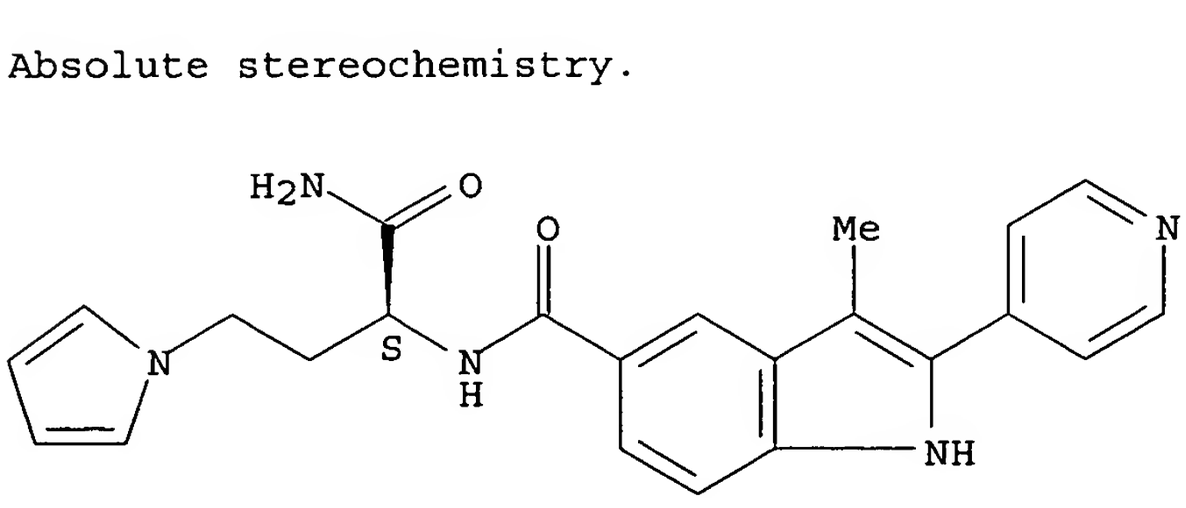
RN 336857-92-2 HCAPLUS
CN 1H-Indole-5-carboxamide, N-[(1R)-2-amino-2-oxo-1-[(phenylthio)methyl]ethyl]-3-methyl-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 336857-94-4 HCAPLUS
CN 1H-Indole-5-carboxamide, N-[(1S)-1-(aminocarbonyl)-3-(1H-pyrrol-1-yl)propyl]-3-methyl-2-(4-pyridinyl)-, mono(trifluoroacetate) (9CI) (CA INDEX NAME)

Absolute stereochemistry.

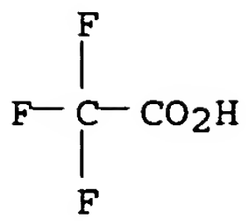


CM 1

CRN 336857-93-3
CMF C23 H23 N5 O2

CM 2

CRN 76-05-1
CMF C2 H F3 O2

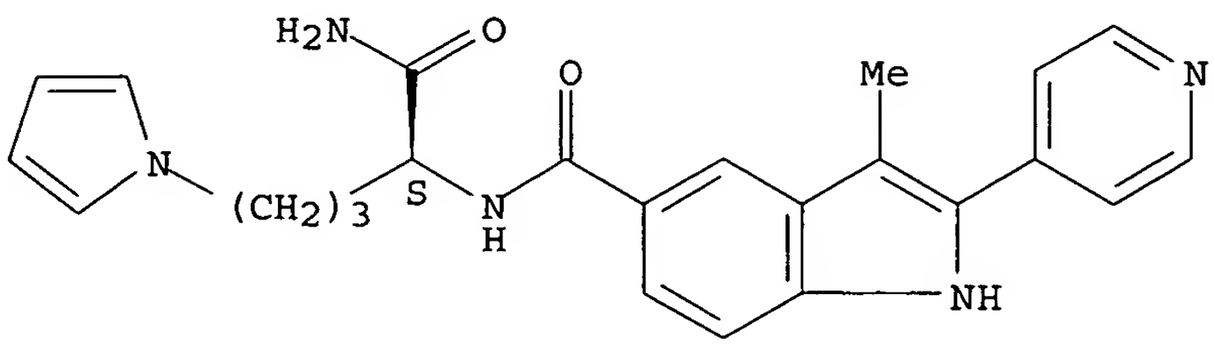


RN 336857-96-6 HCAPLUS
CN 1H-Indole-5-carboxamide, N-[(1S)-1-(aminocarbonyl)-4-(1H-pyrrol-1-yl)butyl]-3-methyl-2-(4-pyridinyl)-, monoacetate (9CI) (CA INDEX NAME)

CM 1

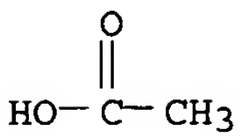
CRN 336857-95-5
CMF C24 H25 N5 O2

Absolute stereochemistry.



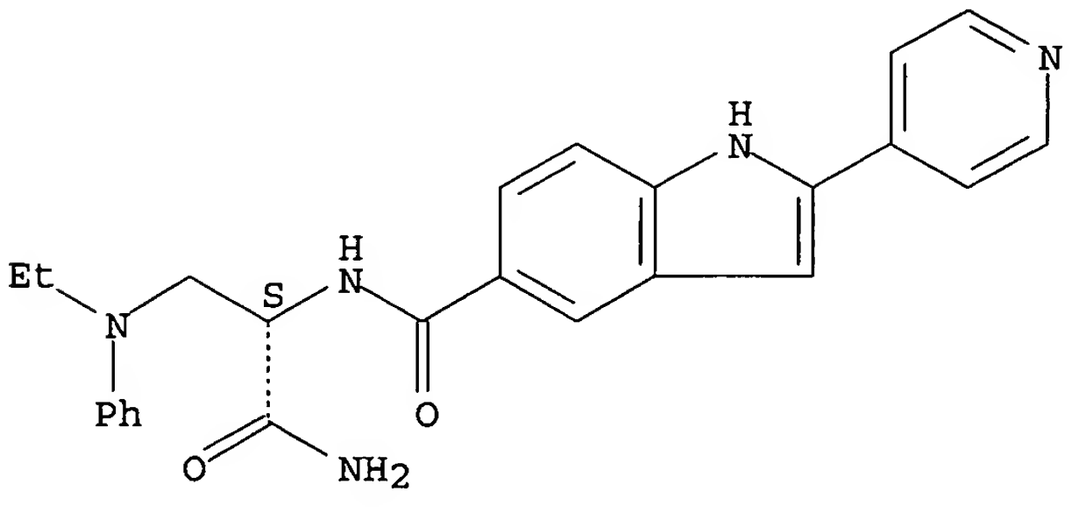
CM 2

CRN 64-19-7
CMF C2 H4 O2



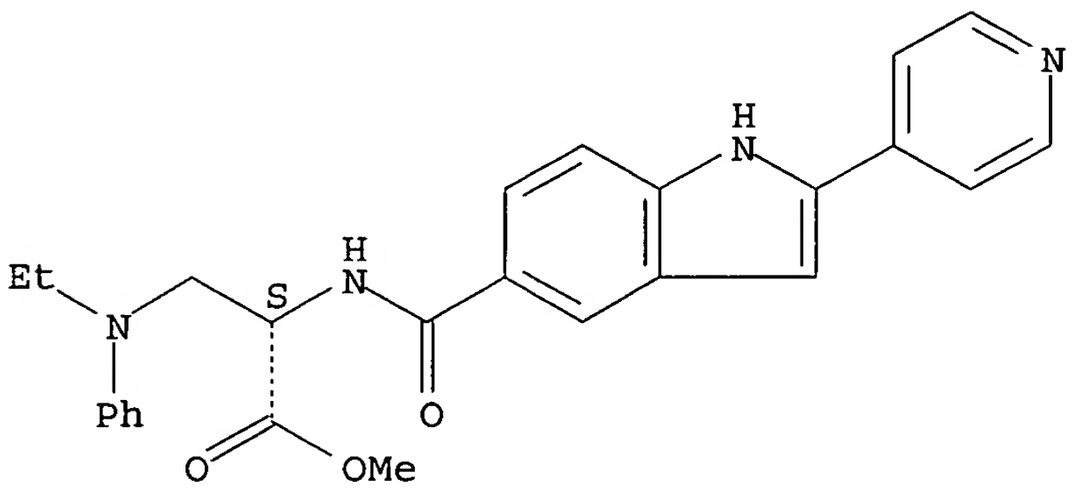
RN 336857-97-7 HCAPLUS
CN 1H-Indole-5-carboxamide, N-[(1S)-2-amino-1-[(ethylphenylamino)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **336858-04-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of amino acid indolecarboxamides as modulators of NFκB activity)
RN 336858-04-9 HCAPLUS
CN L-Alanine, 3-(ethylphenylamino)-N-[[2-(4-pyridinyl)-1H-indol-5-yl]carbonyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:12443 HCAPLUS
DOCUMENT NUMBER: 134:86539
TITLE: Preparation of benzimidazolecarboxylic acid amino acid amides as Iκ B **kinase** inhibitors.
INVENTOR(S): Ritzeler, Olaf; Stilz, Hans Ulrich; Neises, Bernhard; Bock, William Jerome, Jr.; Walser, Armin; Flynn, Gary A.
PATENT ASSIGNEE(S): Aventis Pharma Deutschland GmbH, Germany
SOURCE: PCT Int. Appl., 102 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001000610	A1	20010104	WO 2000-EP5340	20000609
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
DE 19928424	A1	20001228	DE 1999-19928424	19990623
DE 10006297	A1	20010816	DE 2000-10006297	20000212
CA 2377085	AA	20010104	CA 2000-2377085	20000609

BR 2000012450	A	20020402	BR 2000-12450		20000609
EP 1194425	A1	20020410	EP 2000-938780		20000609
EP 1194425	B1	20050810			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
JP 2003503400	T2	20030128	JP 2001-507019		20000609
EE 200100619	A	20030217	EE 2001-619		20000609
NZ 516348	A	20030630	NZ 2000-516348		20000609
AU 769350	B2	20040122	AU 2000-54042		20000609
AT 301651	E	20050815	AT 2000-938780		20000609
RU 2261248	C2	20050927	RU 2002-101485		20000609
NO 2001006154	A	20020219	NO 2001-6154		20011217
HK 1047582	A1	20050304	HK 2002-108645		20021129
PRIORITY APPLN. INFO.:			DE 1999-19928424	A	19990623
			DE 2000-10006297	A	20000212
			WO 2000-EP5340	W	20000609

OTHER SOURCE(S): MARPAT 134:86539

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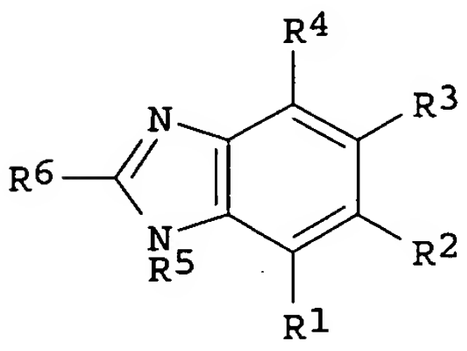

I

AB Title compds. [I; 1 of R1-R4 = DNR8CHR9Z; D = CO, SO, SO2; R8 = H, alkyl; R9 = amino acid residue, (substituted) aryl, heteroaryl, heterocyclyl, alkyl, etc.; Z = (substituted) aryl, heteroaryl, heterocyclyl, etc.; the remainder of R1-R4 = H, halo, alkyl, (substituted) heteroaryl, heterocyclyl, alkyl, cyano, aralkoxy, alkoxy, etc.; R5 = H, OH, O; R6 = (substituted) aryl, Ph, heteroaryl, heterocyclyl], were prepared Thus, 2-pyrid-4-ylbenzimidazol-4-carboxylic acid (preparation given), H-Leu-OMe, TOTU, and (Me2CH)2EtN were stirred in MeCN to give 98% 2-pyrid-4-ylbenzimidazol-4-carbonylleucine Me ester. I inhibited I. **kappa.**B **kinase** with IC50 = 0.07-72 μM.

IT **313064-84-5P 313064-85-6P 313064-86-7P**
313064-87-8P 313064-88-9P 313064-91-4P
313064-92-5P 313064-93-6P 313064-94-7P
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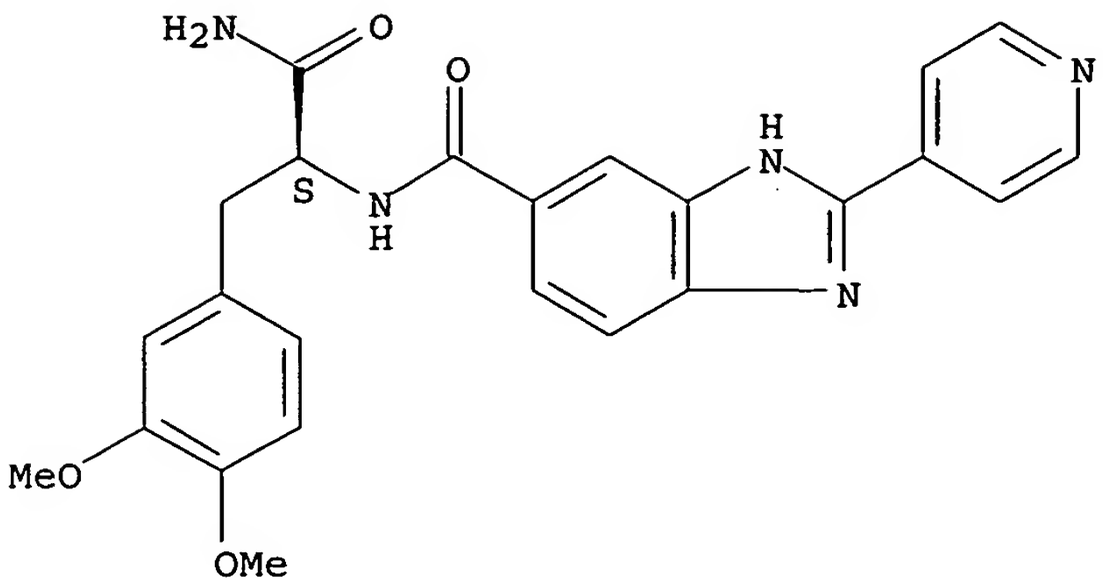
316833-08-6P 316833-09-7P 316833-10-0P
316833-11-1P 316833-12-2P 316833-13-3P
316833-14-4P 316833-15-5P 316833-16-6P
316833-17-7P 316833-18-8P 316833-19-9P
316833-20-2P 316833-21-3P 316833-22-4P
316833-23-5P 316833-24-6P 316833-25-7P
316833-26-8P 316833-28-0P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of benzimidazolecarboxylic acid amino acid amides as I κ B **kinase** inhibitors)

RN 313064-84-5 HCAPLUS

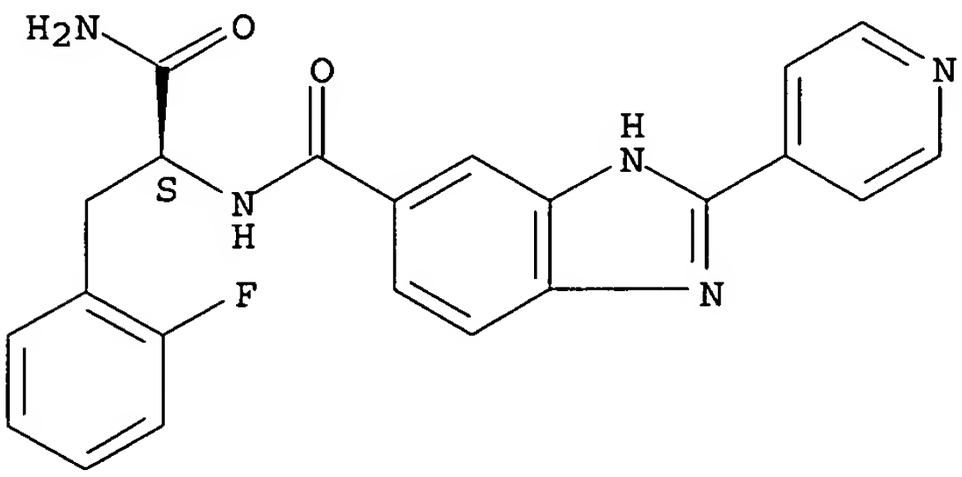
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-2-amino-1-[(3,4-dimethoxyphenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



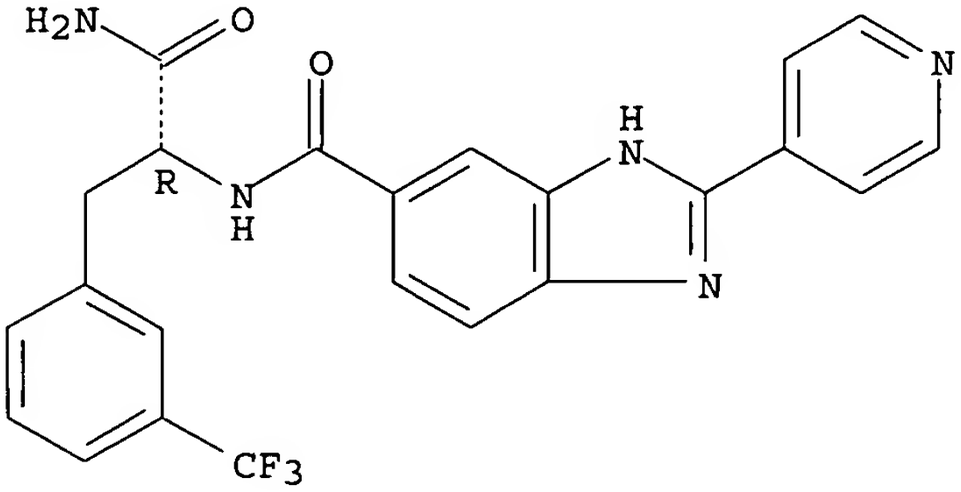
RN 313064-85-6 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-2-amino-1-[(2-fluorophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



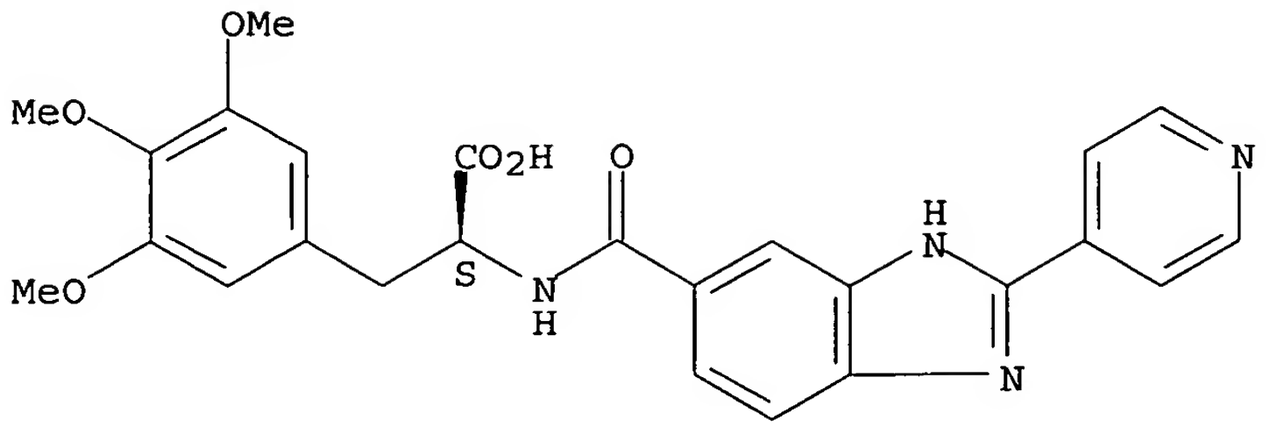
RN 313064-86-7 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1R)-2-amino-2-oxo-1-[[3-(trifluoromethyl)phenyl]methyl]ethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



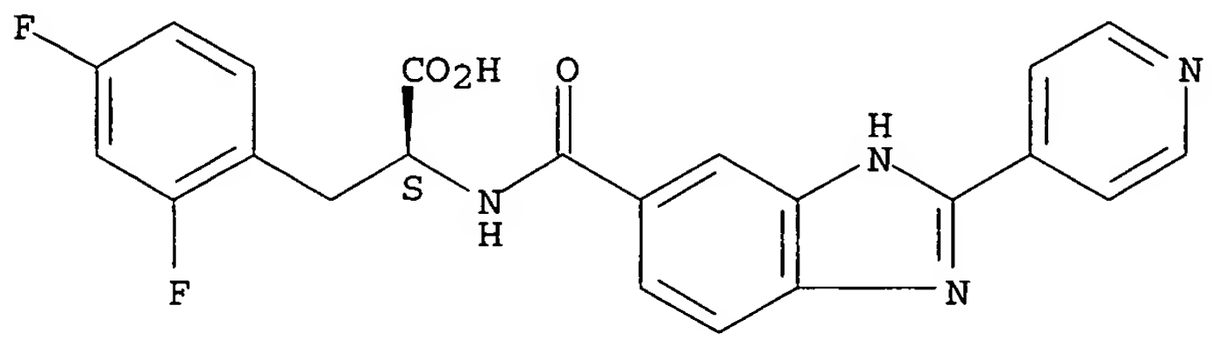
RN 313064-87-8 HCAPLUS
CN L-Tyrosine, 3,5-dimethoxy-O-methyl-N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



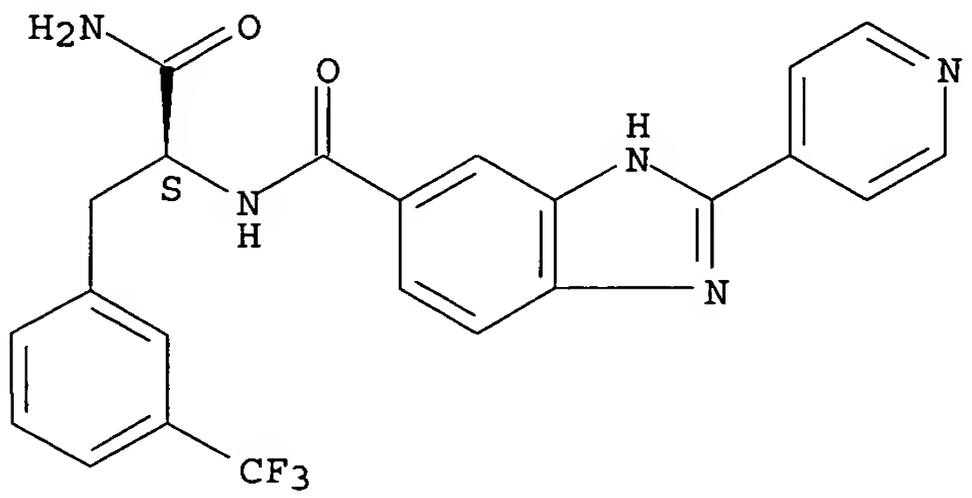
RN 313064-88-9 HCAPLUS
CN L-Phenylalanine, 2,4-difluoro-N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



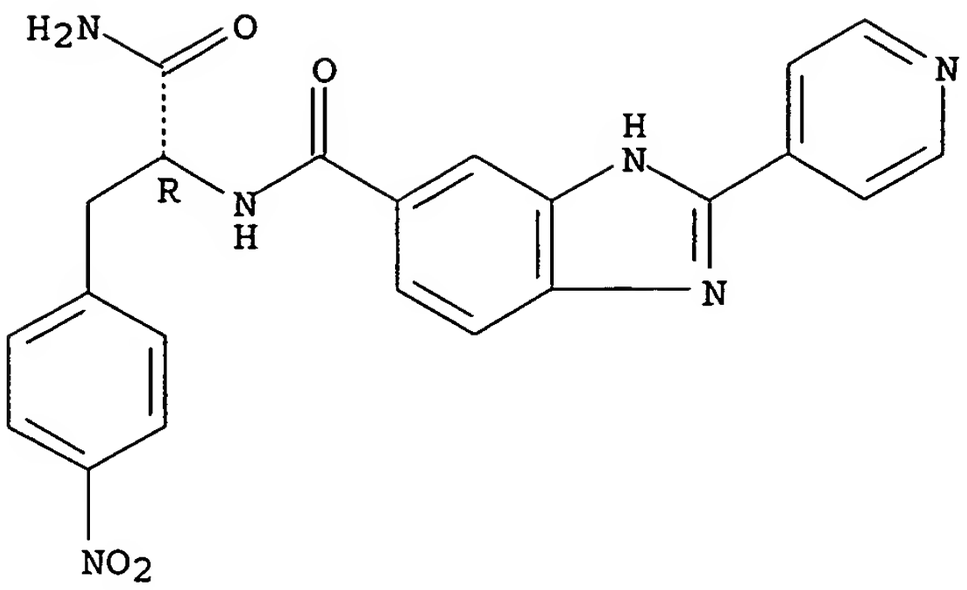
RN 313064-91-4 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-2-amino-2-oxo-1-[[3-(trifluoromethyl)phenyl]methyl]ethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

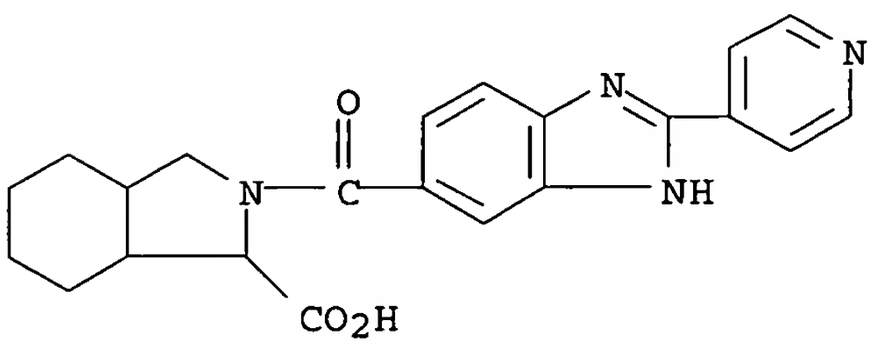


RN 313064-92-5 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1R)-2-amino-1-[(4-nitrophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

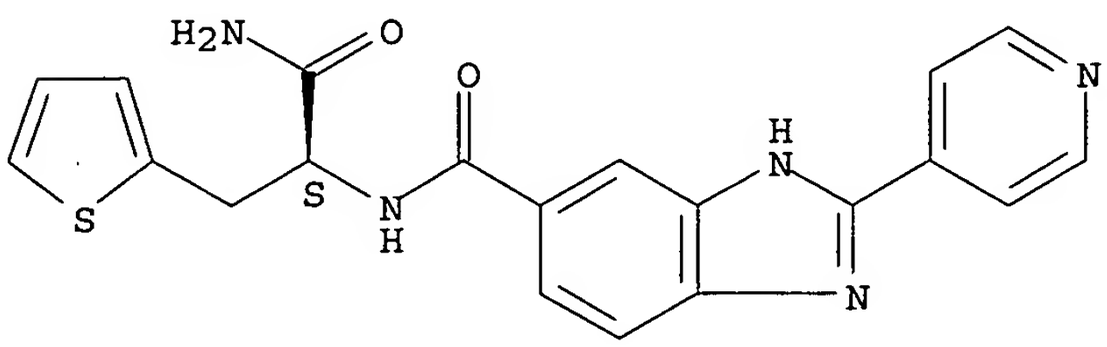


RN 313064-93-6 HCAPLUS
CN 1H-Isoindole-1-carboxylic acid, octahydro-2-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]- (9CI) (CA INDEX NAME)



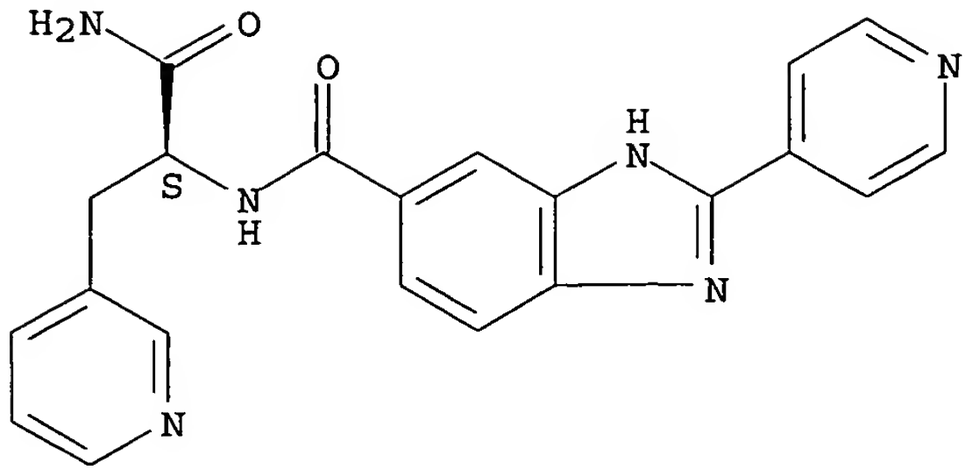
RN 313064-94-7 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-2-amino-2-oxo-1-(2-thienylmethyl)ethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



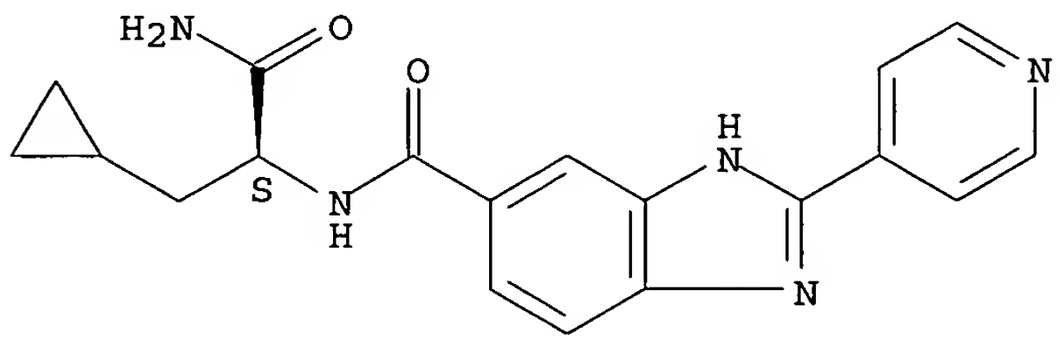
RN 313064-95-8 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-2-amino-2-oxo-1-(3-pyridinylmethyl)ethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



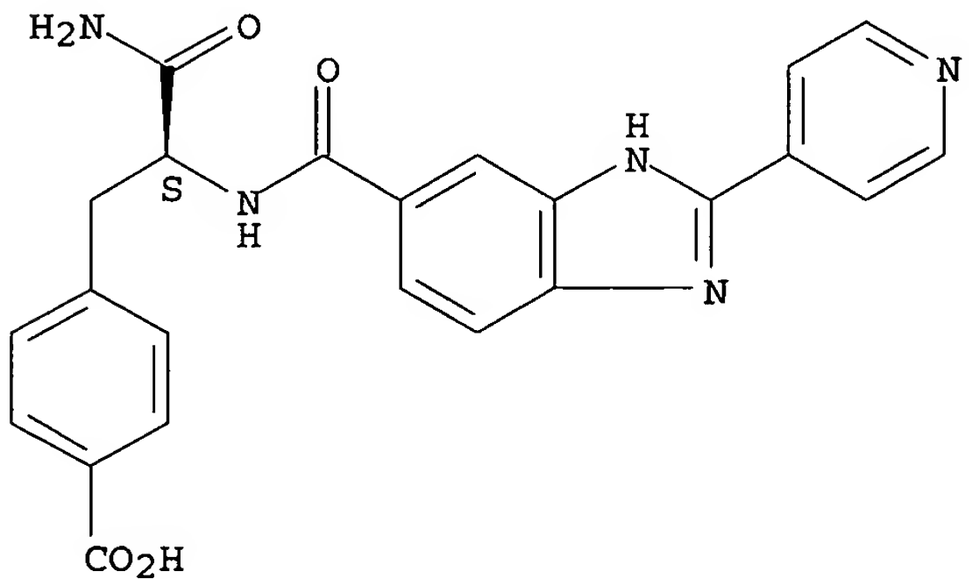
RN 313064-96-9 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-2-amino-1-(cyclopropylmethyl)-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



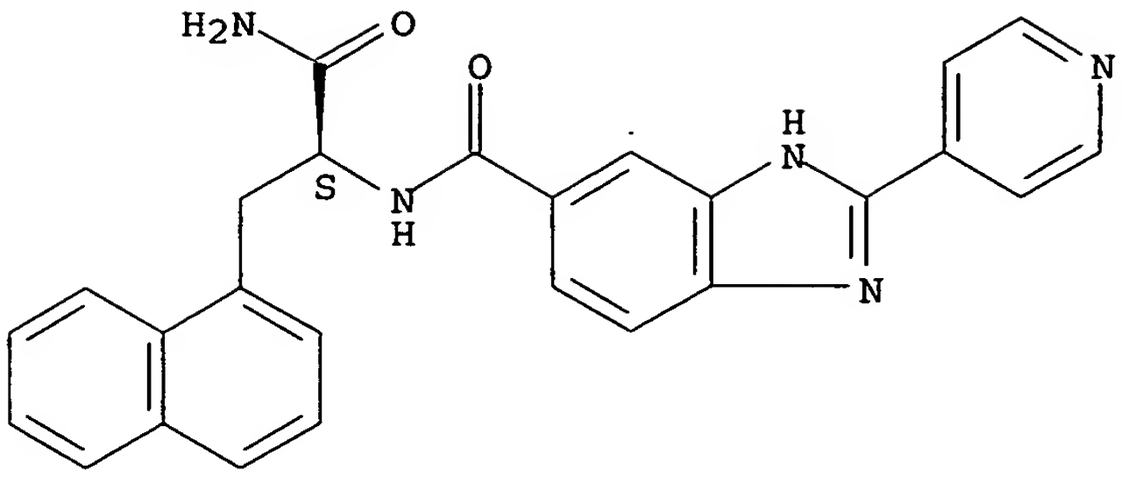
RN 313064-97-0 HCAPLUS
CN Benzoic acid, 4-[(2S)-3-amino-3-oxo-2-[[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]amino]propyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



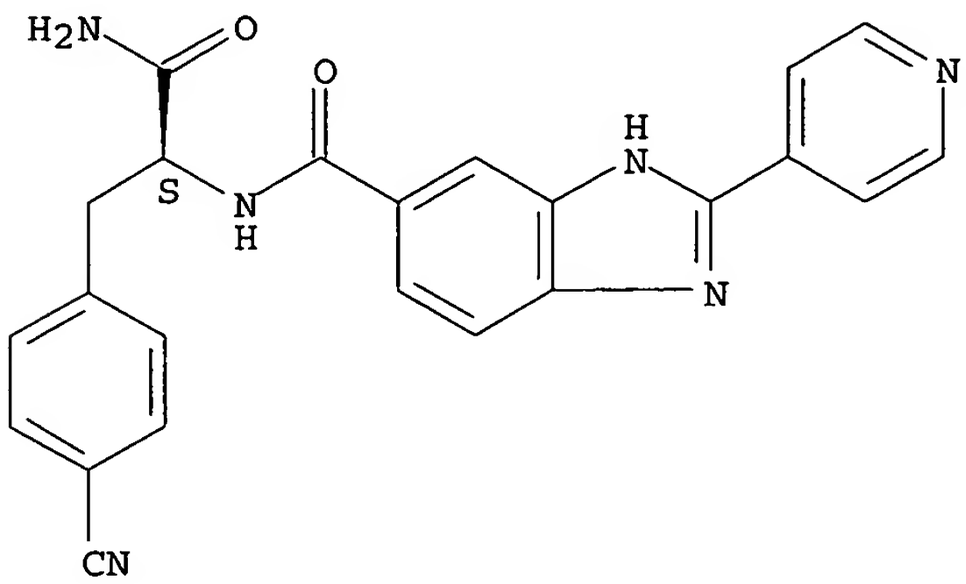
RN 313064-98-1 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-2-amino-1-(1-naphthalenylmethyl)-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



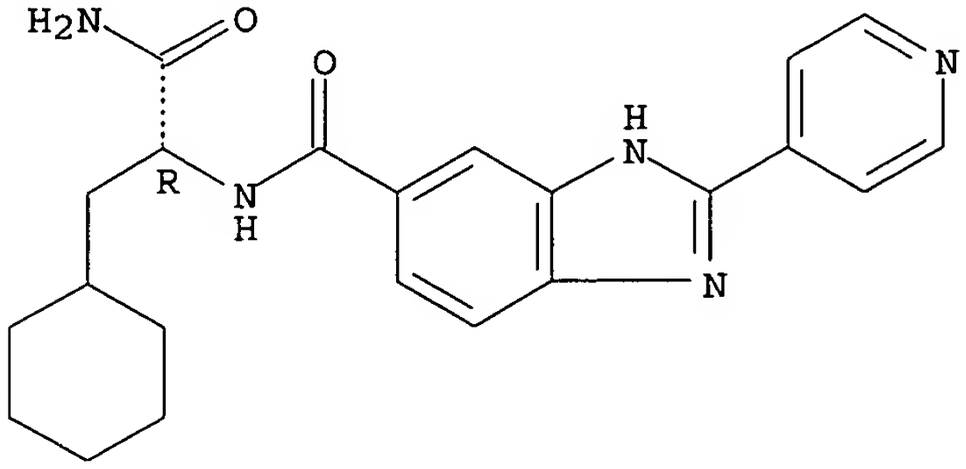
RN 313064-99-2 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-2-amino-1-[(4-cyanophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

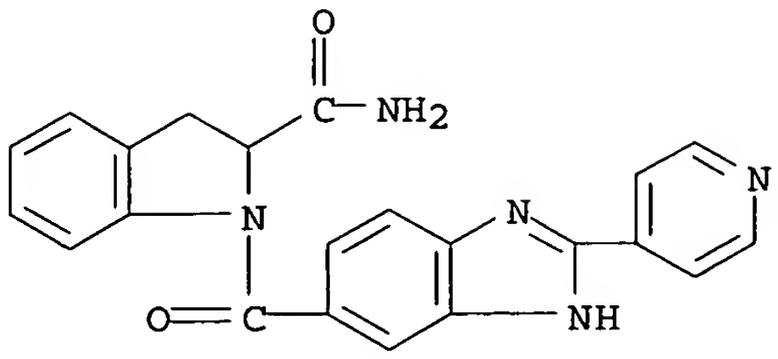


RN 313065-01-9 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1R)-2-amino-1-(cyclohexylmethyl)-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

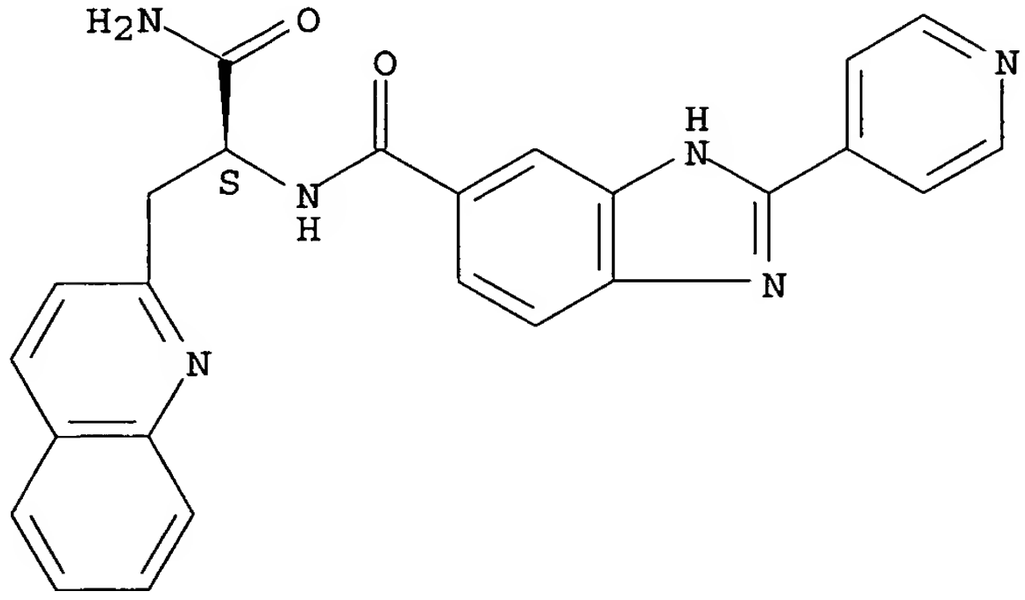


RN 313065-02-0 HCAPLUS
CN 1H-Indole-2-carboxamide, 2,3-dihydro-1-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]- (9CI) (CA INDEX NAME)



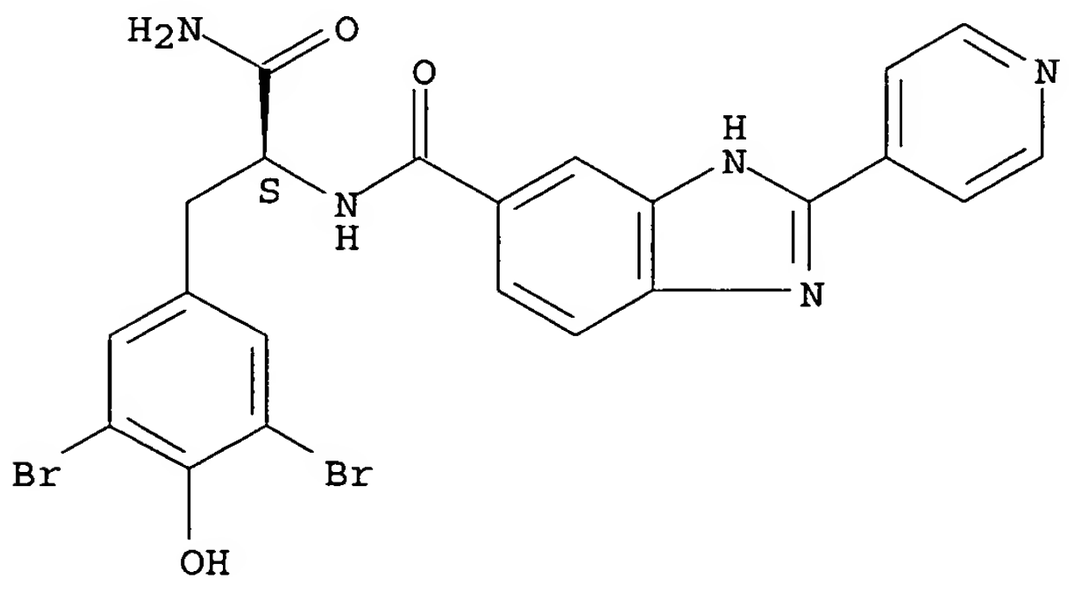
RN 313065-03-1 HCAPLUS
CN 2-Quinolinepropanamide, α-[[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]amino]-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



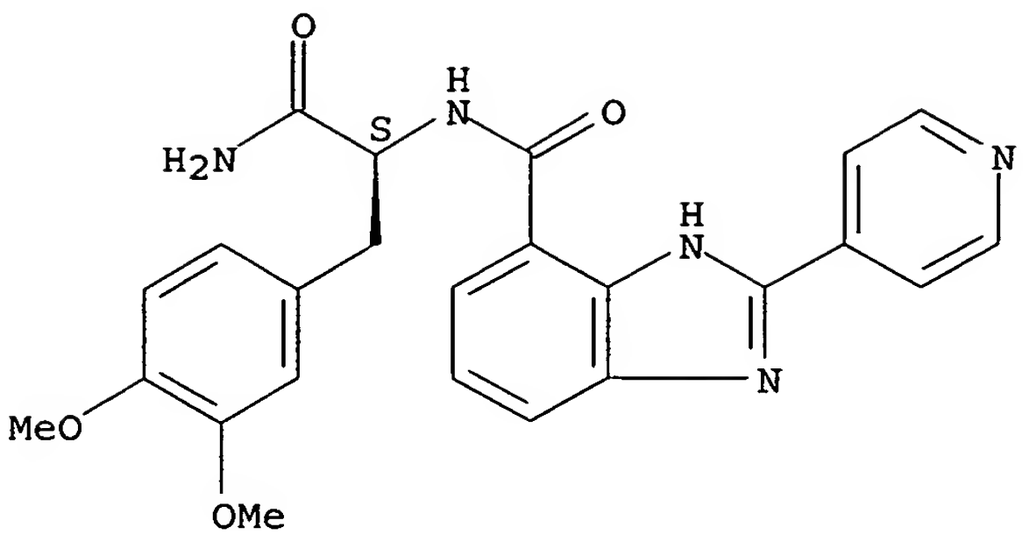
RN 313065-04-2 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-2-amino-1-[(3,5-dibromo-4-hydroxyphenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

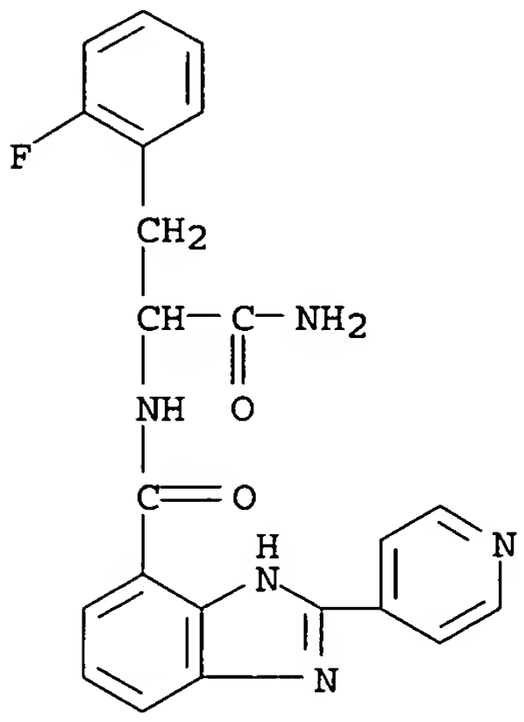


RN 313065-05-3 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-2-amino-1-[(3,4-dimethoxyphenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

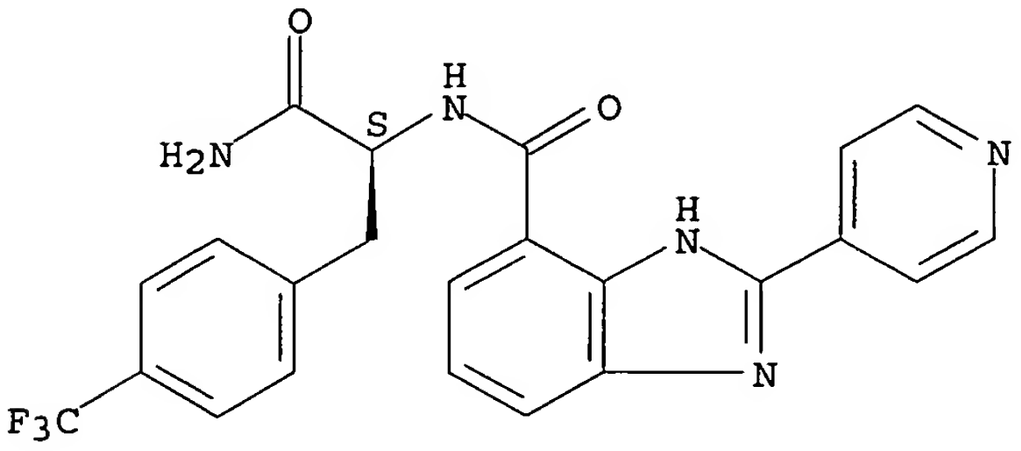


RN 313065-06-4 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[2-amino-1-[(2-fluorophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)



RN 313065-07-5 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-2-amino-2-oxo-1-[[4-(trifluoromethyl)phenyl]methyl]ethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

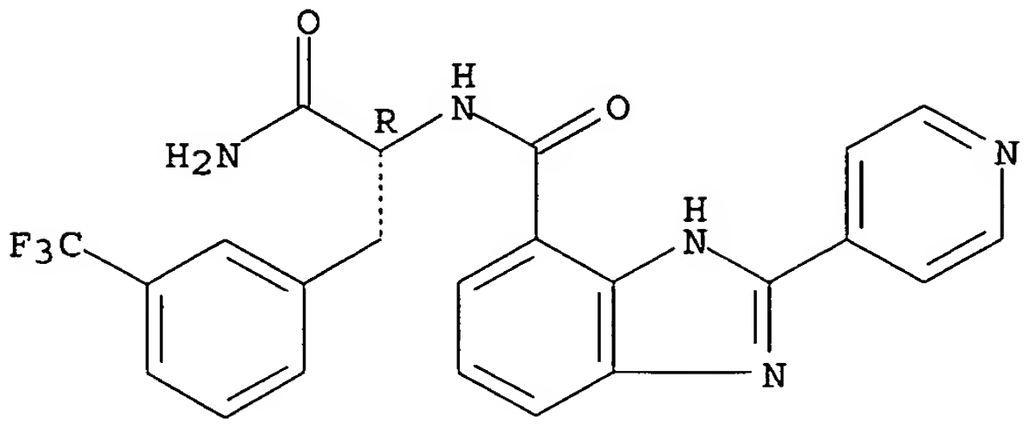
Absolute stereochemistry.



RN 313065-08-6 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1R)-2-amino-2-oxo-1-[[3-(trifluoromethyl)phenyl]methyl]ethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX

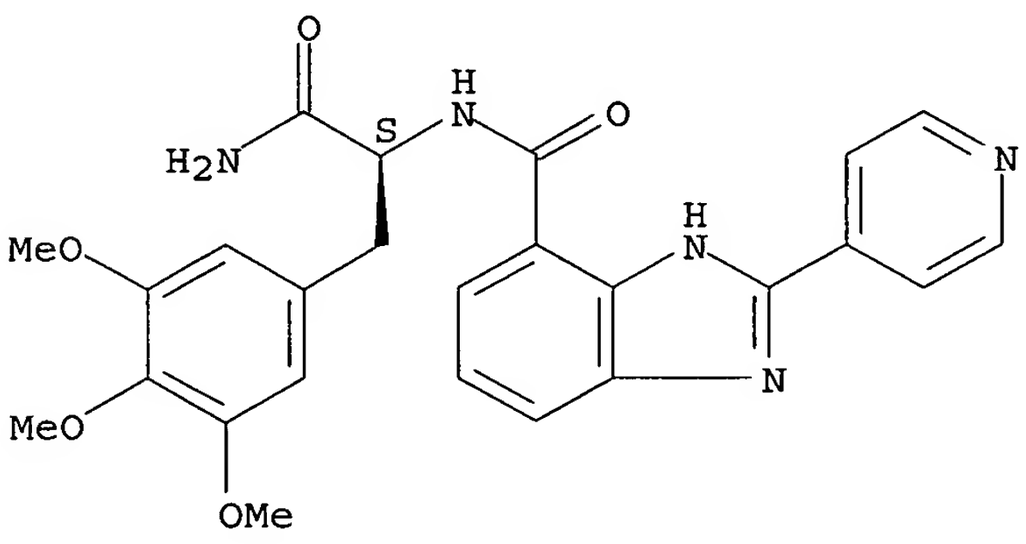
NAME)

Absolute stereochemistry.



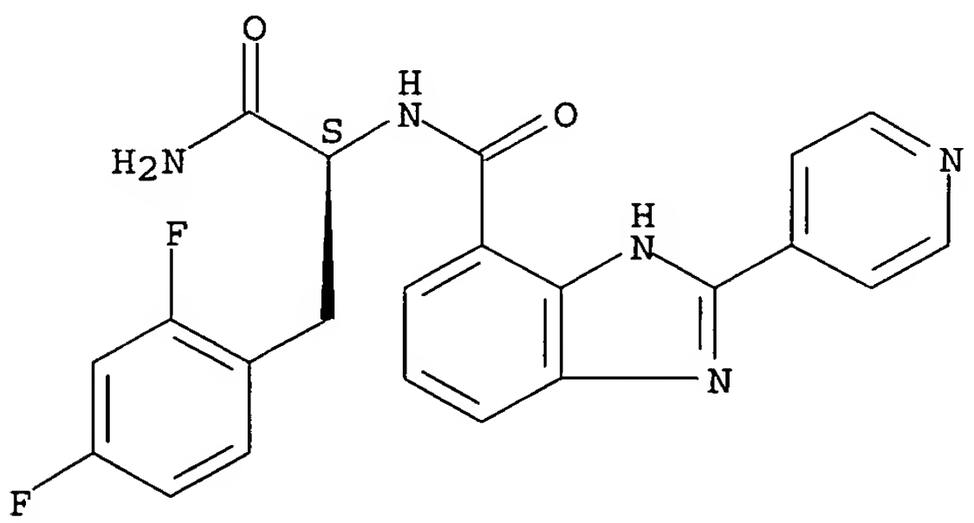
RN 313065-09-7 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-2-amino-2-oxo-1-[(3,4,5-trimethoxyphenyl)methyl]ethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



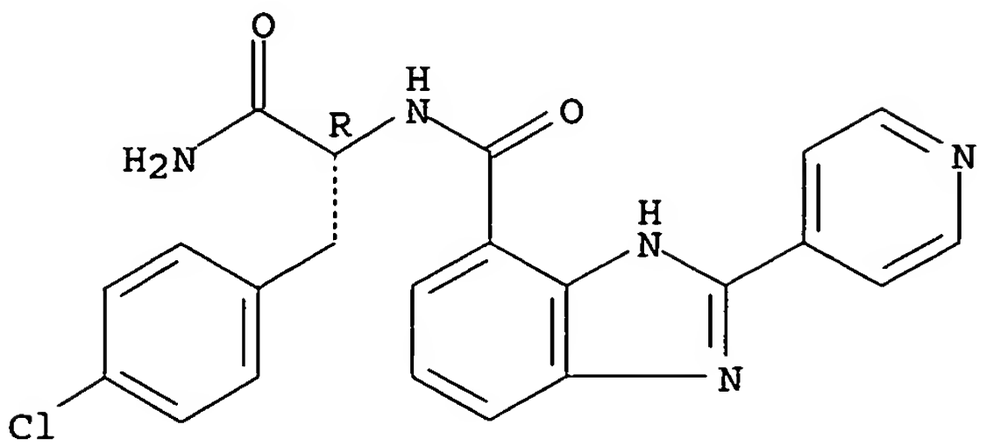
RN 313065-10-0 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-2-amino-1-[(2,4-difluorophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



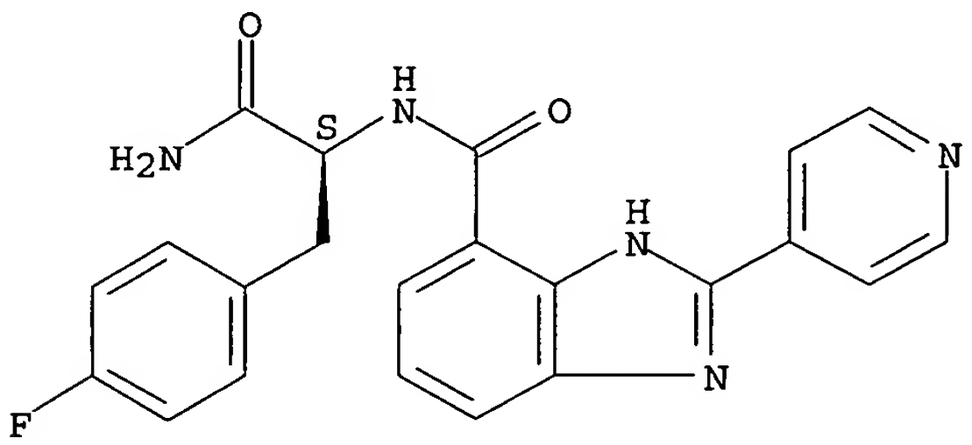
RN 313065-11-1 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1R)-2-amino-1-[(4-chlorophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



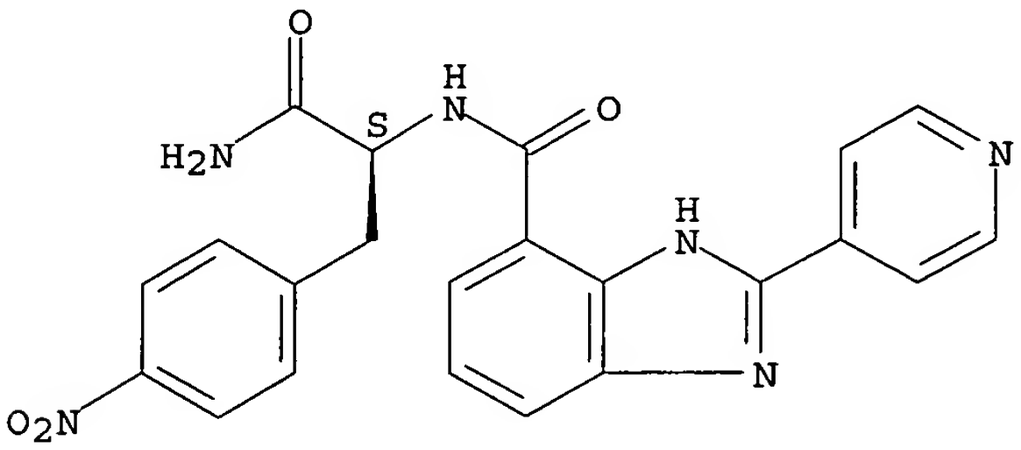
RN 313065-12-2 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-2-amino-1-[(4-fluorophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

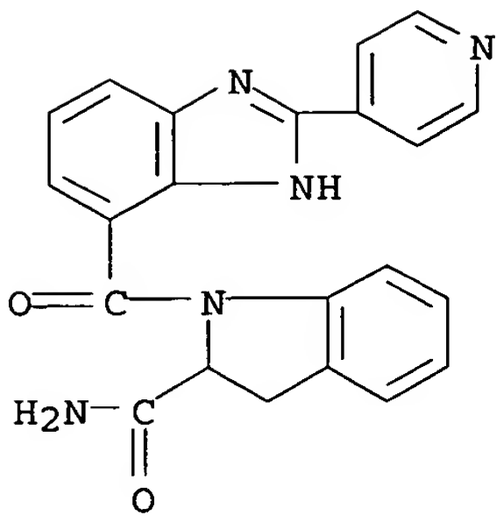


RN 313065-13-3 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-2-amino-1-[(4-nitrophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

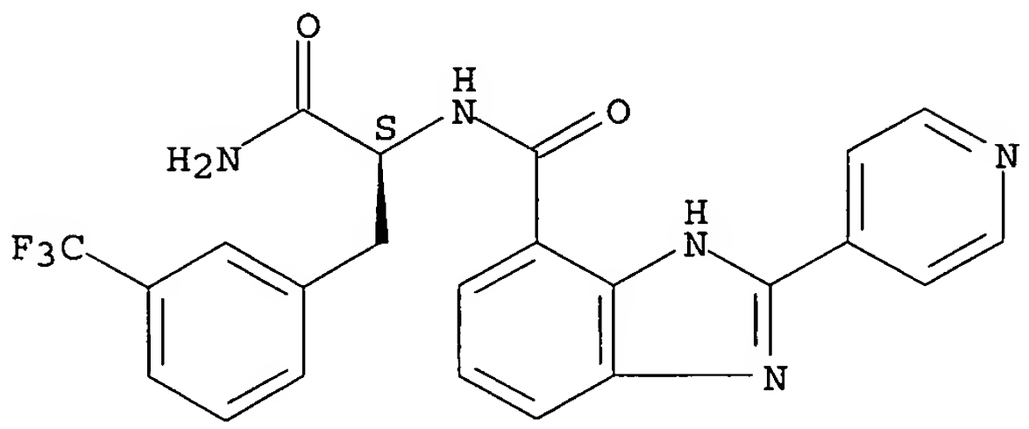


RN 313065-14-4 HCAPLUS
CN 1H-Indole-2-carboxamide, 2,3-dihydro-1-[[2-(4-pyridinyl)-1H-benzimidazol-4-yl]carbonyl]- (9CI) (CA INDEX NAME)



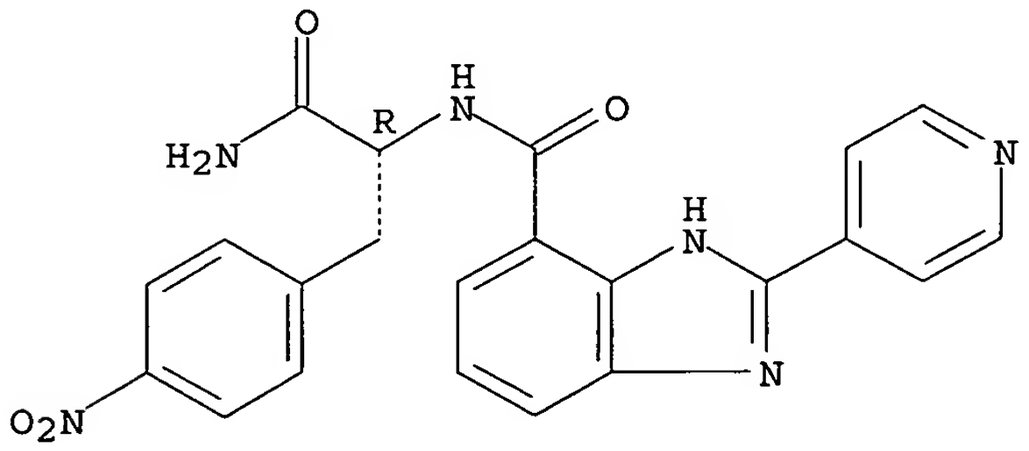
RN 313065-15-5 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-2-amino-2-oxo-1-[[3-(trifluoromethyl)phenyl]methyl]ethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

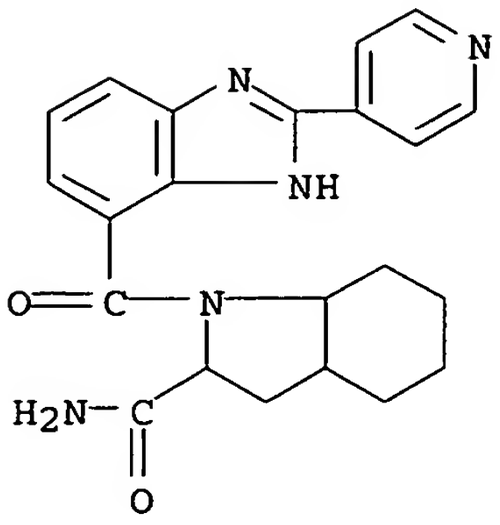


RN 313065-16-6 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1R)-2-amino-1-[(4-nitrophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

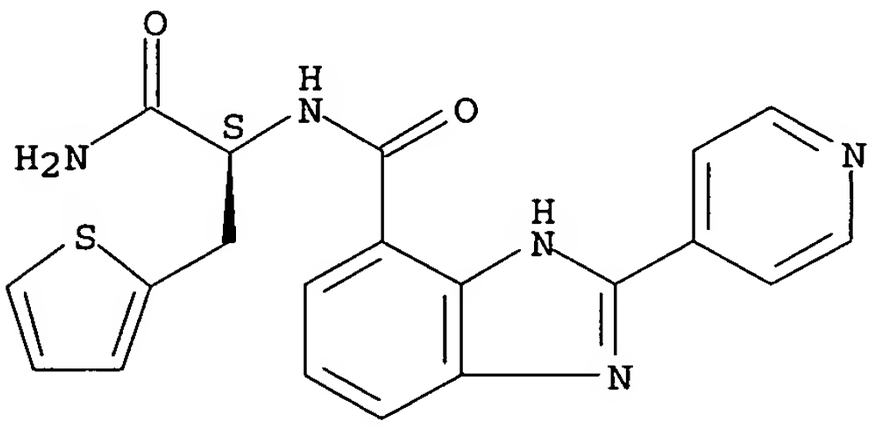


RN 313065-17-7 HCAPLUS
CN 1H-Indole-2-carboxamide, octahydro-1-[[2-(4-pyridinyl)-1H-benzimidazol-4-yl]carbonyl]- (9CI) (CA INDEX NAME)



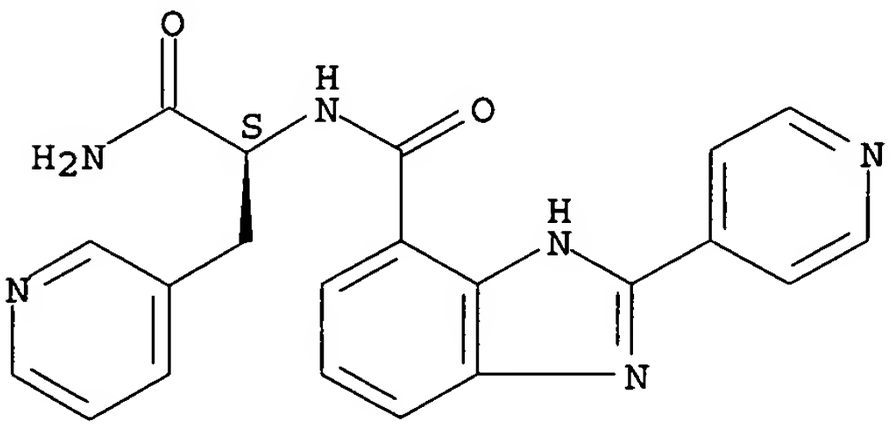
RN 313065-18-8 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-2-amino-2-oxo-1-(2-thienylmethyl)ethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



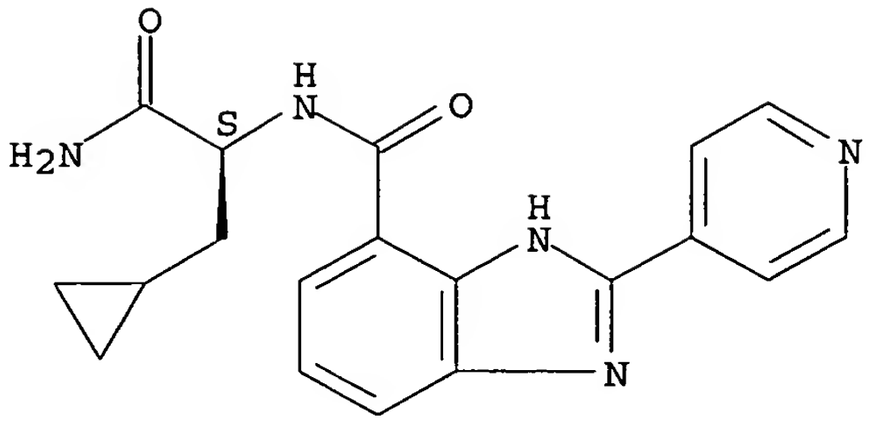
RN 313065-19-9 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-2-amino-2-oxo-1-(3-pyridinylmethyl)ethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



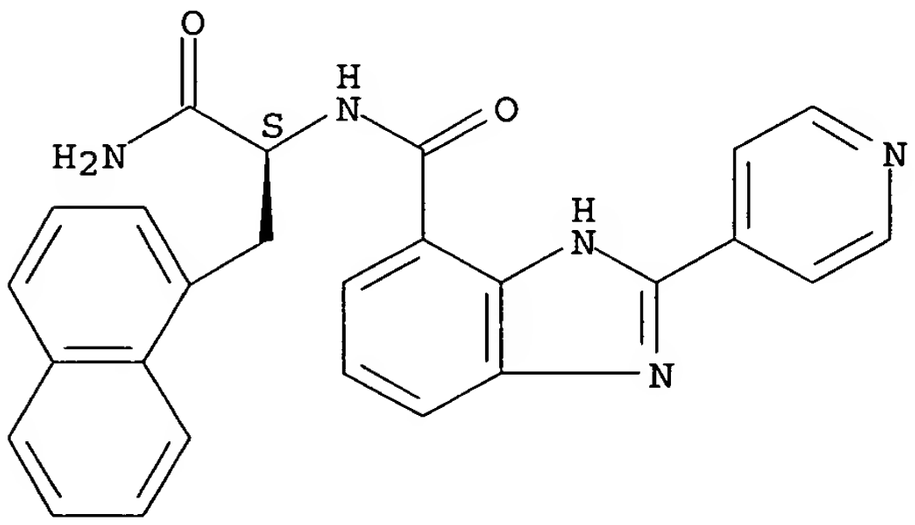
RN 313065-20-2 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-2-amino-1-(cyclopropylmethyl)-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



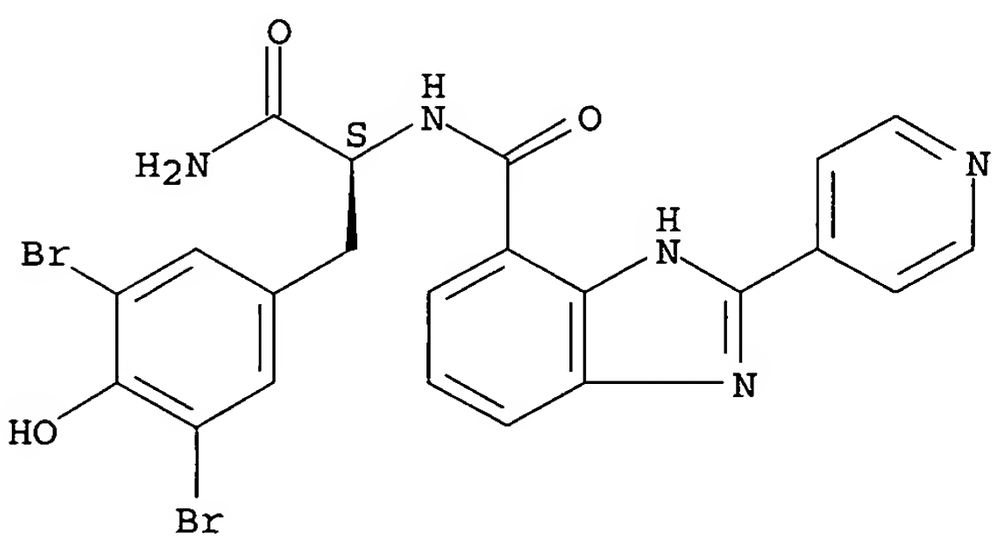
RN 313065-22-4 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-2-amino-1-(1-naphthalenylmethyl)-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



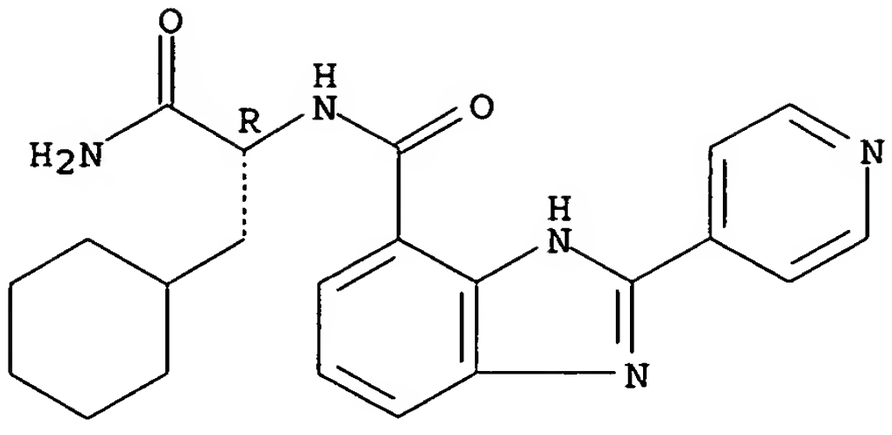
RN 313065-25-7 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-2-amino-1-[(3,5-dibromo-4-hydroxyphenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



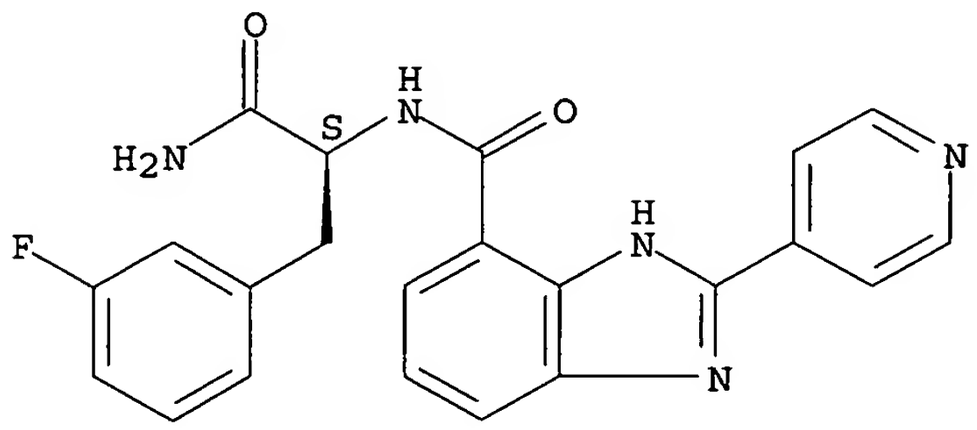
RN 313065-26-8 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1R)-2-amino-1-(cyclohexylmethyl)-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



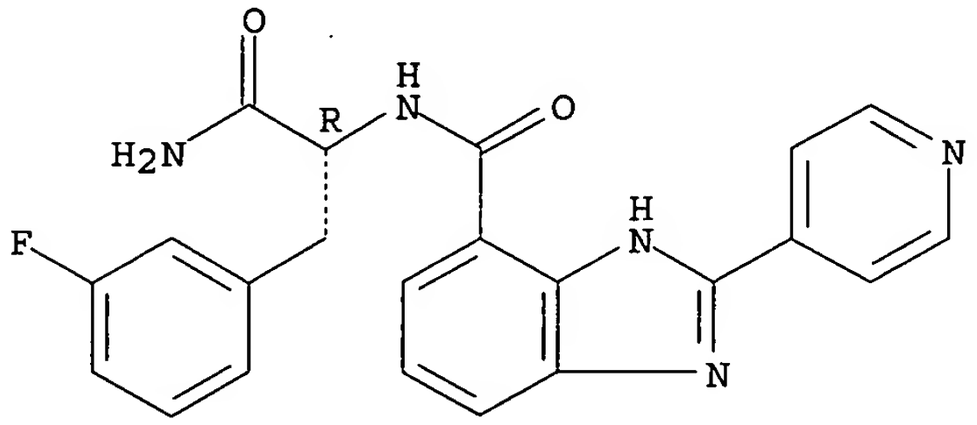
RN 313065-27-9 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-2-amino-1-[(3-fluorophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



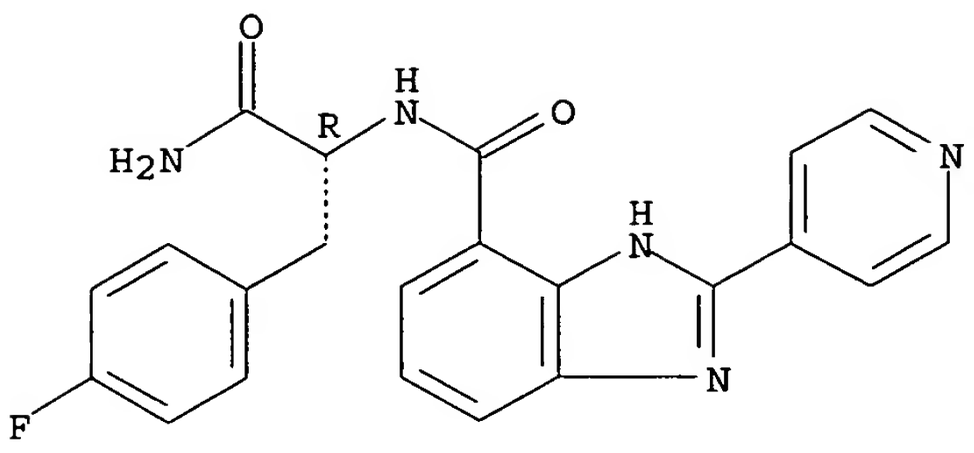
RN 313065-28-0 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1R)-2-amino-1-[(3-fluorophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



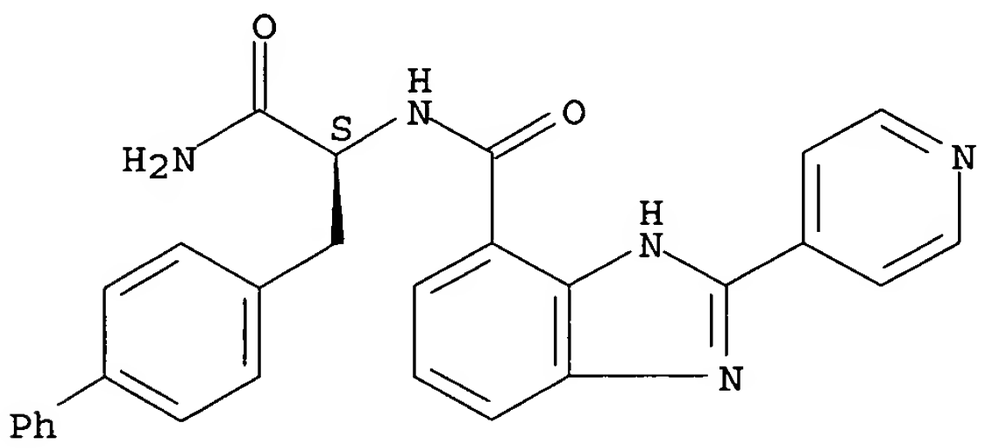
RN 313065-29-1 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1R)-2-amino-1-[(4-fluorophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

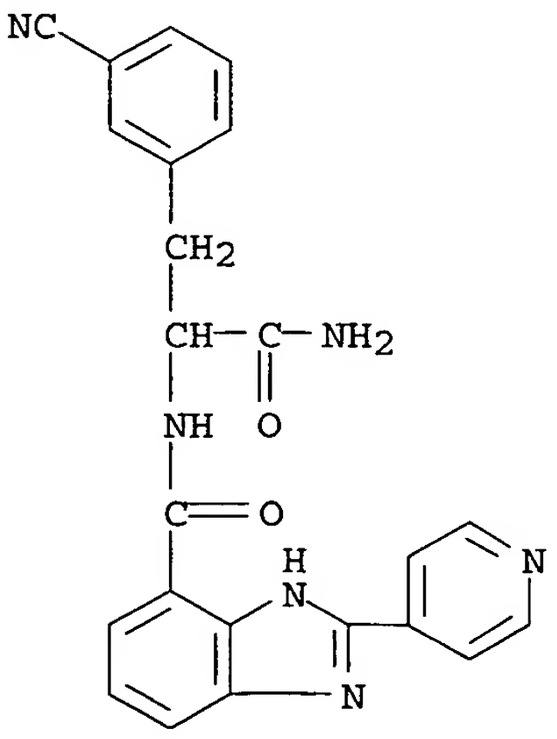


RN 313065-30-4 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-2-amino-1-([1,1'-biphenyl]-4-ylmethyl)-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

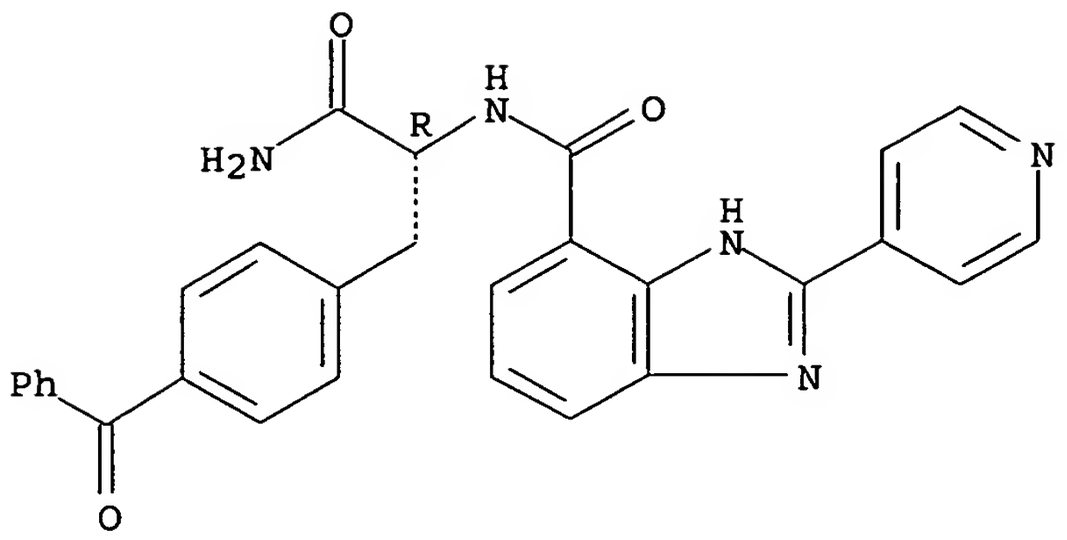


RN 313065-31-5 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[2-amino-1-[(3-cyanophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)



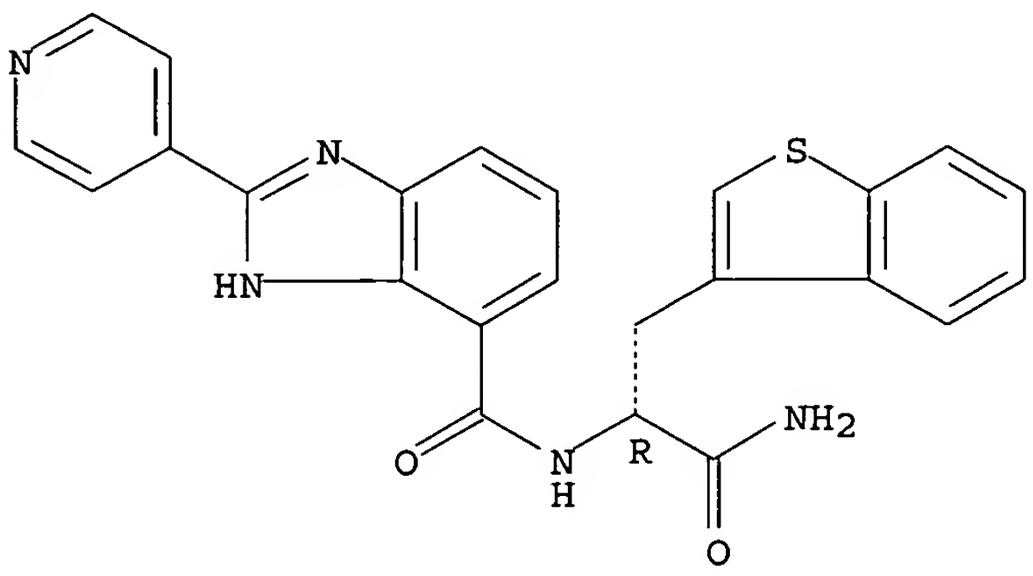
RN 313065-32-6 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1R)-2-amino-1-[(4-benzoylphenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

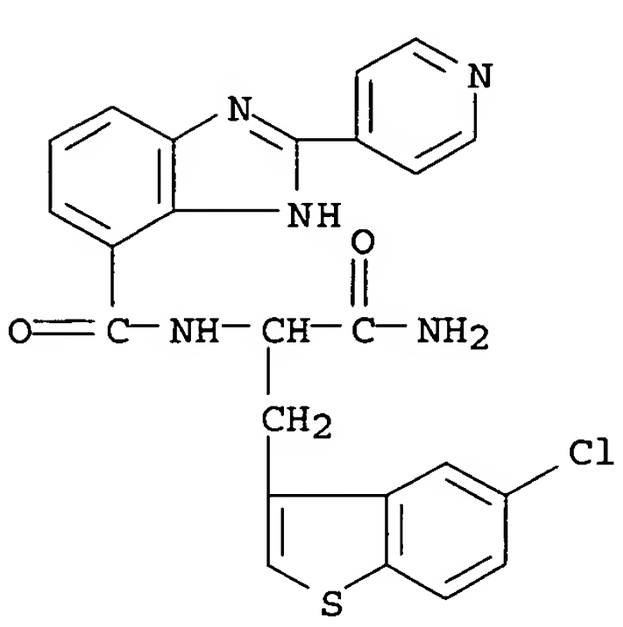


RN 313065-33-7 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1R)-2-amino-1-(benzo[b]thien-3-ylmethyl)-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

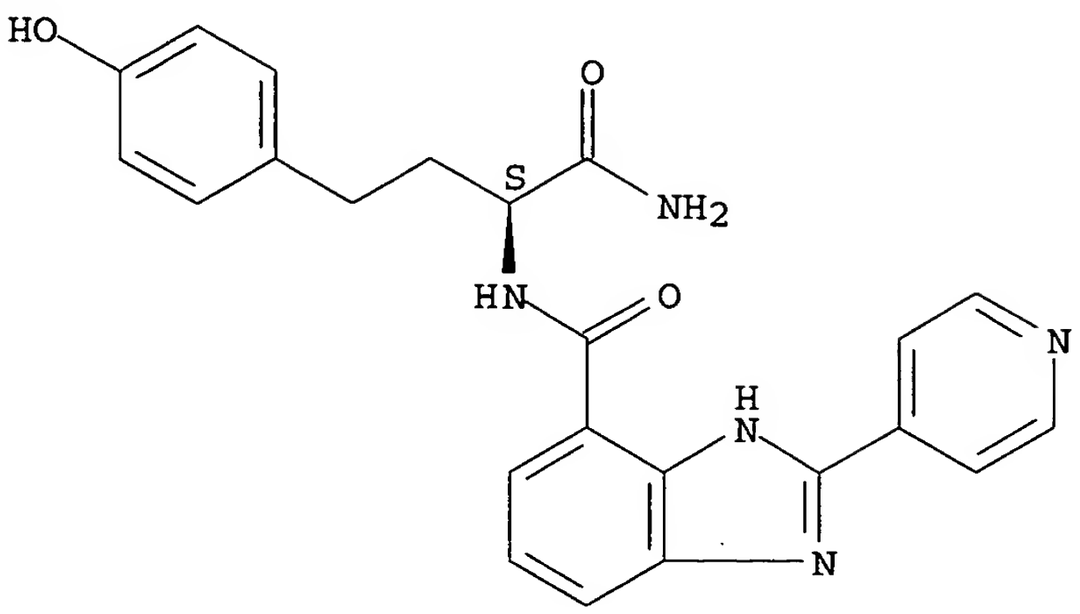


RN 313065-34-8 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[2-amino-1-[(5-chlorobenzo[b]thien-3-yl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)



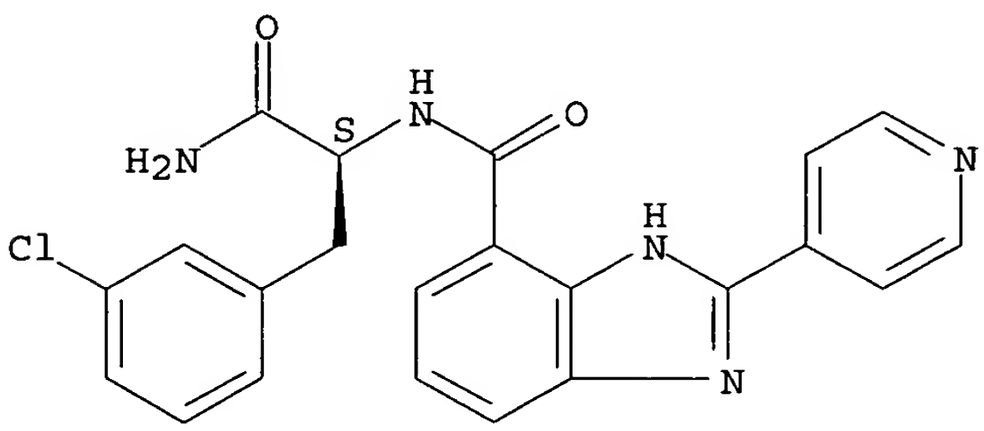
RN 313065-35-9 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-1-(aminocarbonyl)-3-(4-hydroxyphenyl)propyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



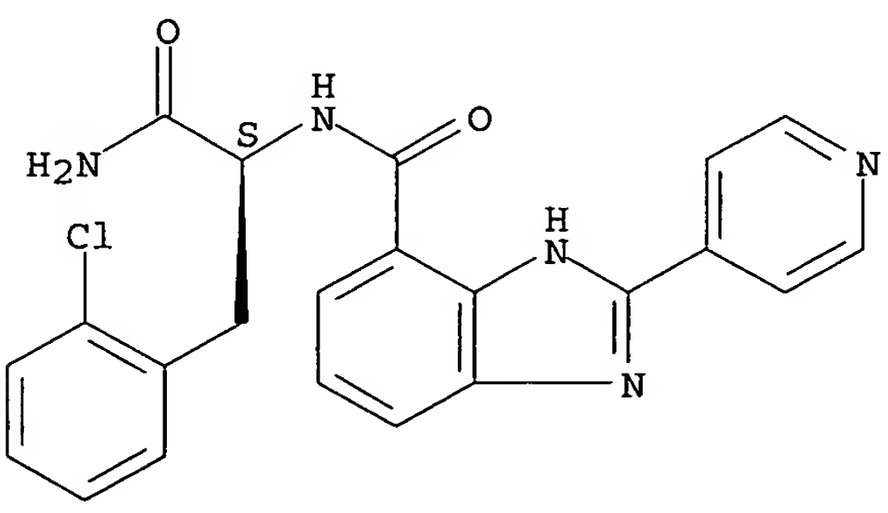
RN 313065-36-0 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-2-amino-1-[(3-chlorophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



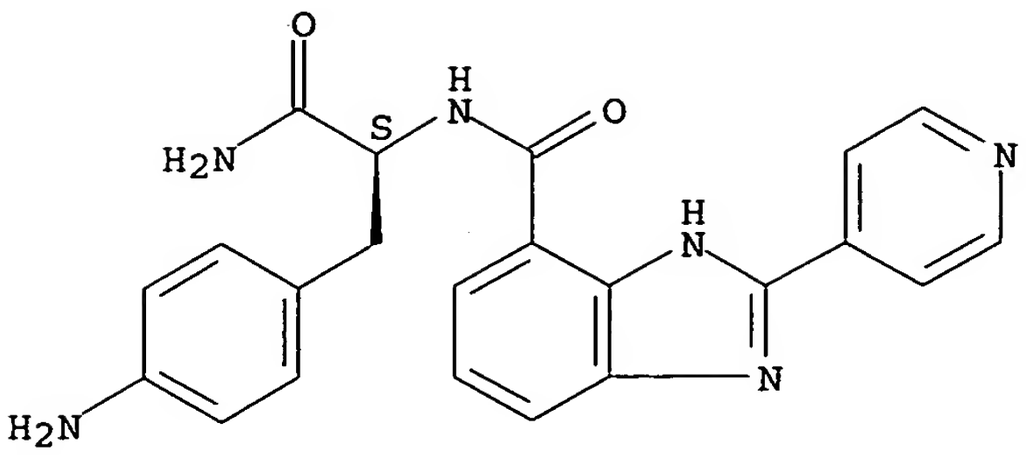
RN 313065-37-1 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-2-amino-1-[(2-chlorophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



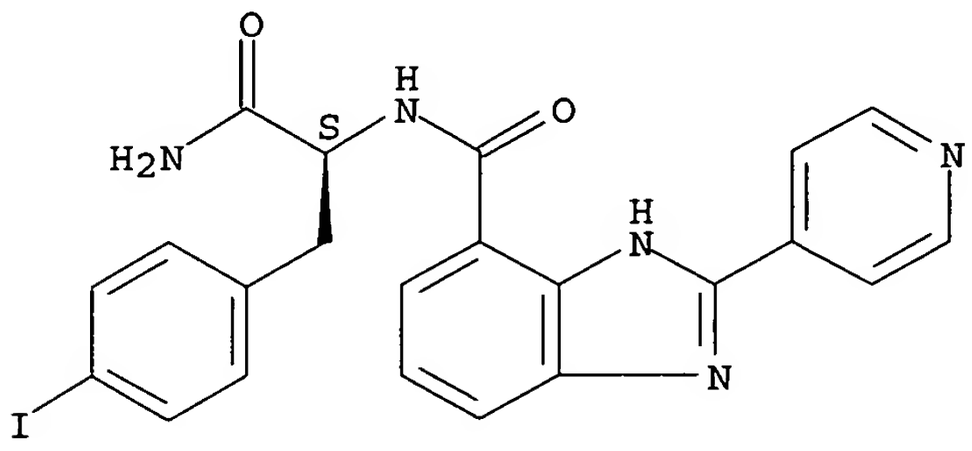
RN 313065-38-2 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-2-amino-1-[(4-aminophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



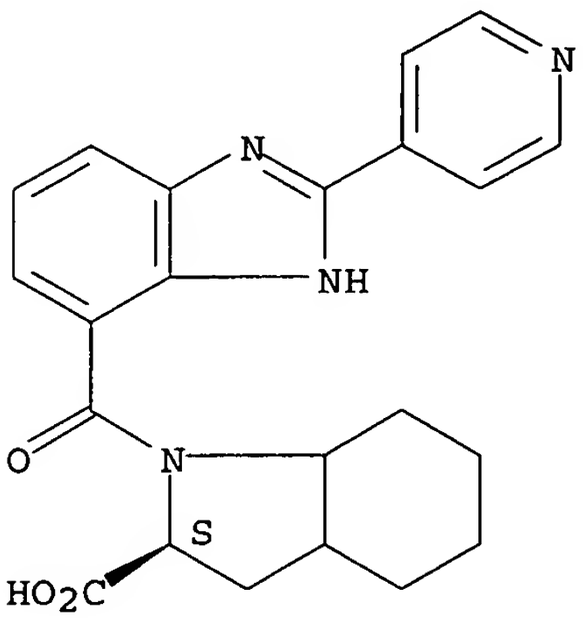
RN 313065-39-3 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-2-amino-1-[(4-iodophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

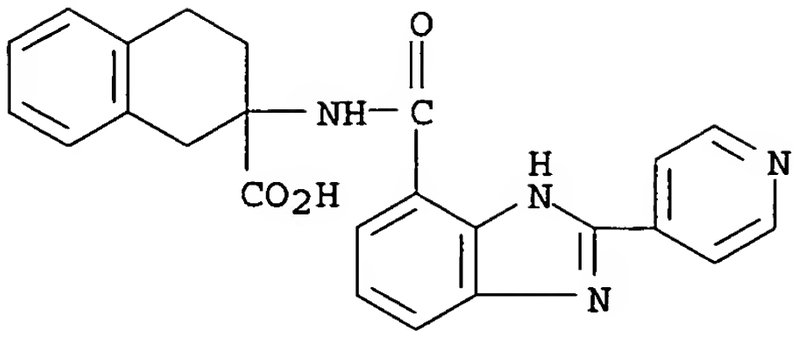


RN 313065-40-6 HCAPLUS
CN 1H-Indole-2-carboxylic acid, octahydro-1-[[2-(4-pyridinyl)-1H-benzimidazol-4-yl]carbonyl]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

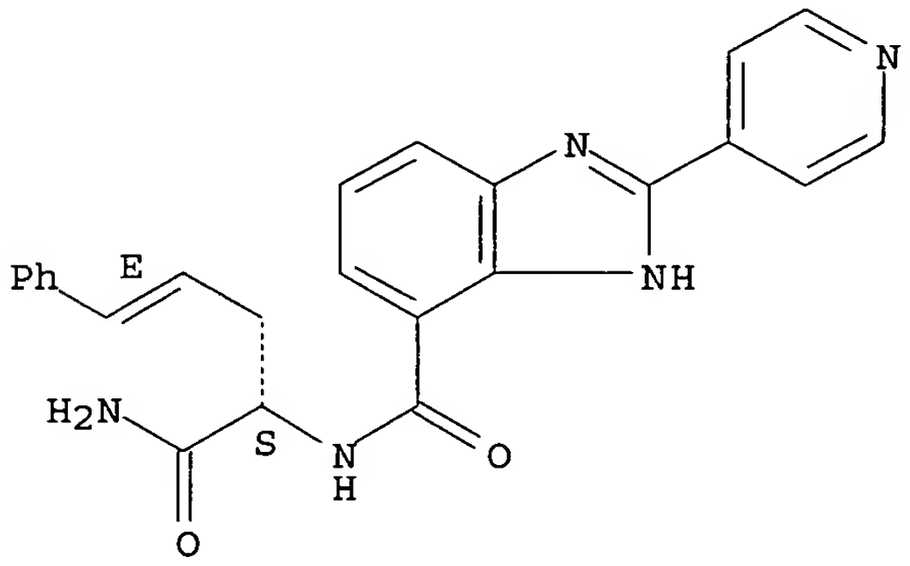


RN 313065-41-7 HCAPLUS
CN 2-Naphthalenecarboxylic acid, 1,2,3,4-tetrahydro-2-[[[2-(4-pyridinyl)-1H-benzimidazol-4-yl]carbonyl]amino]- (9CI) (CA INDEX NAME)



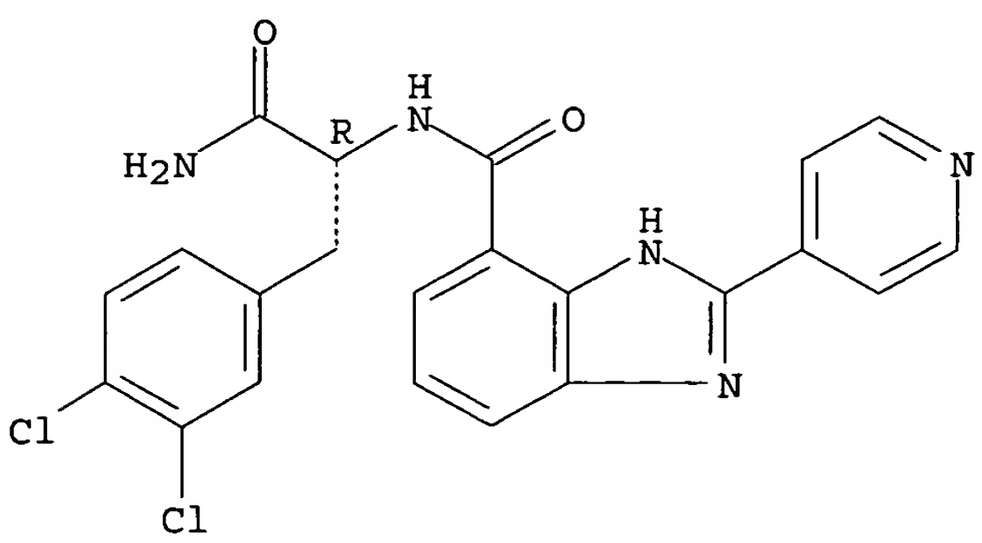
RN 313065-42-8 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S,3E)-1-(aminocarbonyl)-4-phenyl-3-butenyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



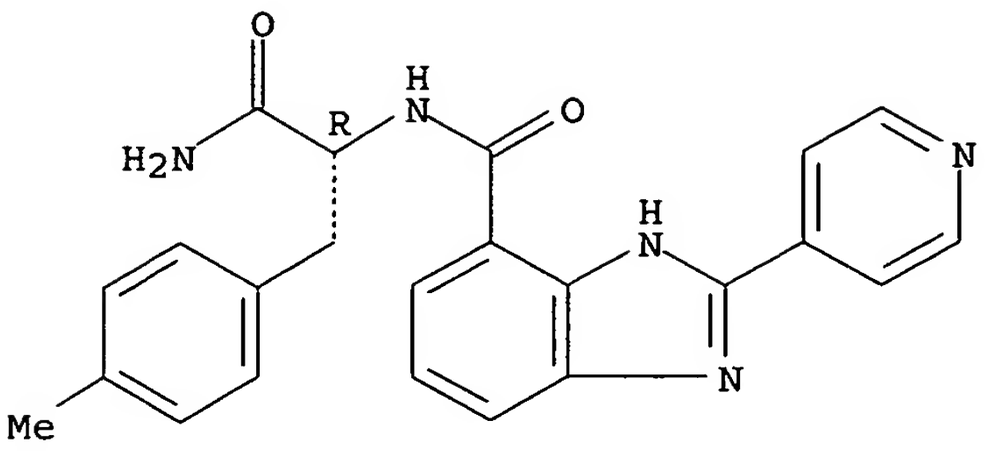
RN 313065-43-9 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1R)-2-amino-1-[(3,4-dichlorophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



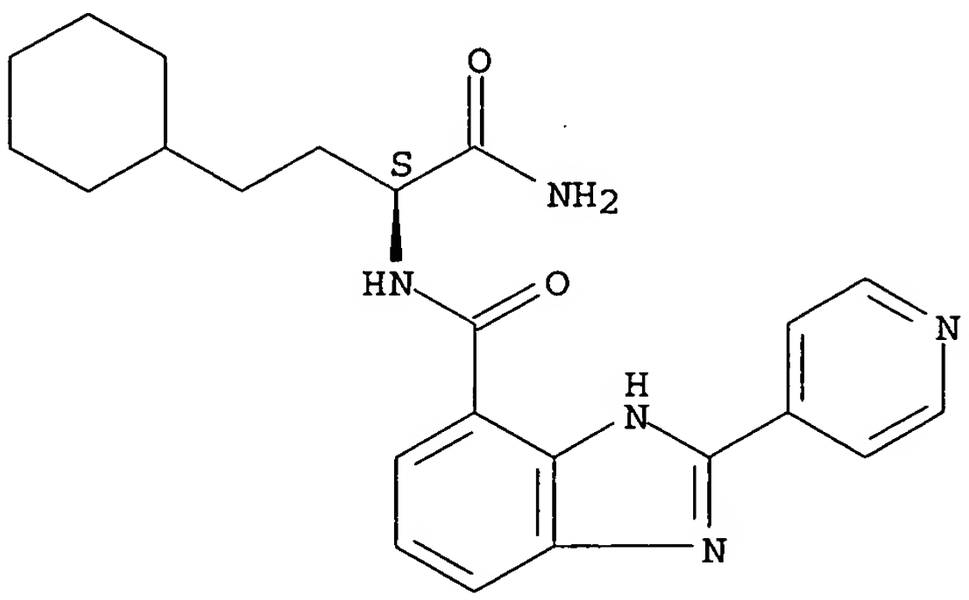
RN 313065-44-0 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1R)-2-amino-1-[(4-methylphenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



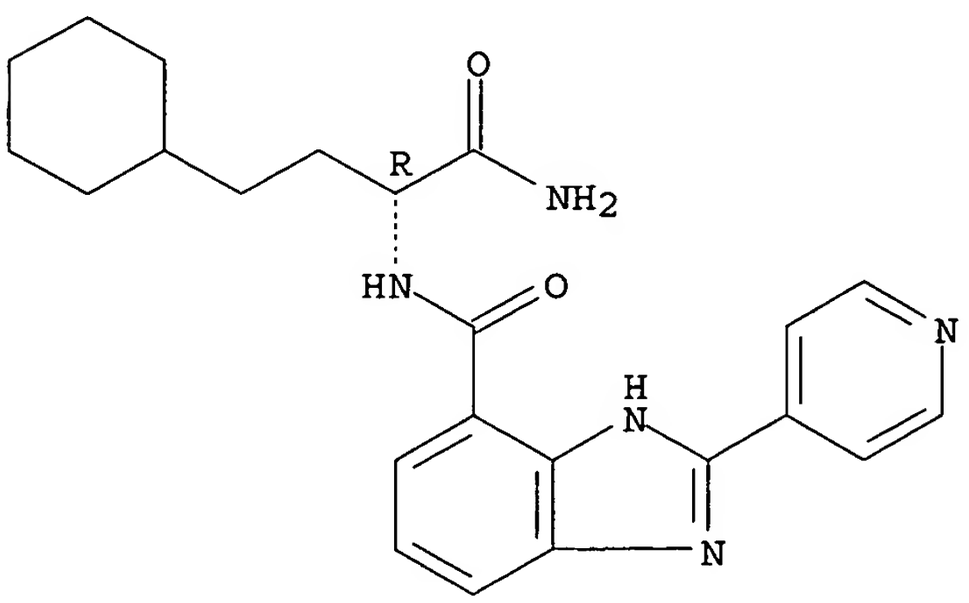
RN 313065-45-1 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-1-(aminocarbonyl)-3-cyclohexylpropyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



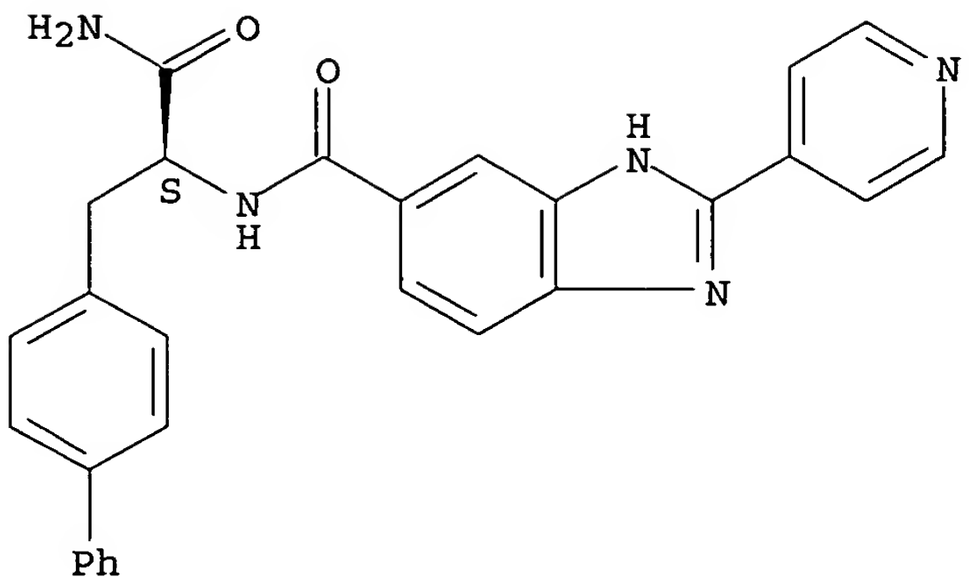
RN 313065-46-2 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1R)-1-(aminocarbonyl)-3-cyclohexylpropyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



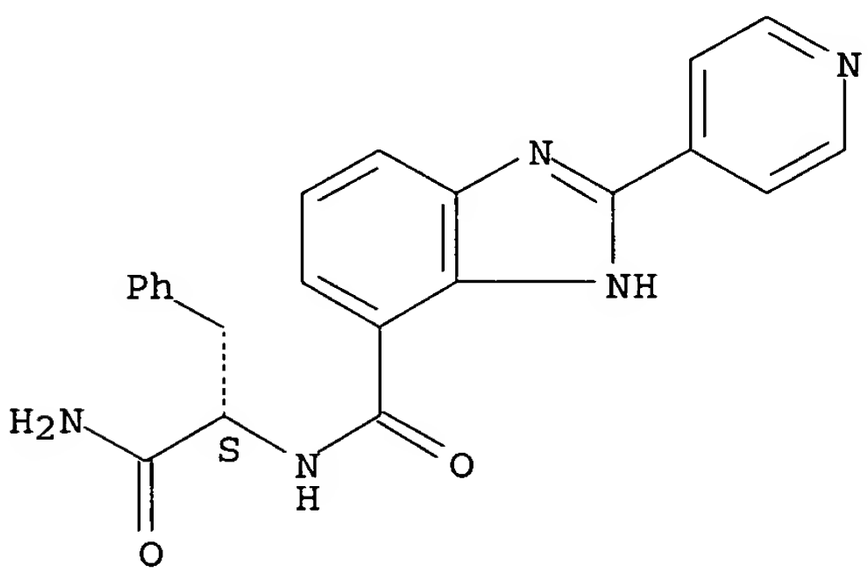
RN 313065-47-3 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-2-amino-1-([1,1'-biphenyl]-4-ylmethyl)-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



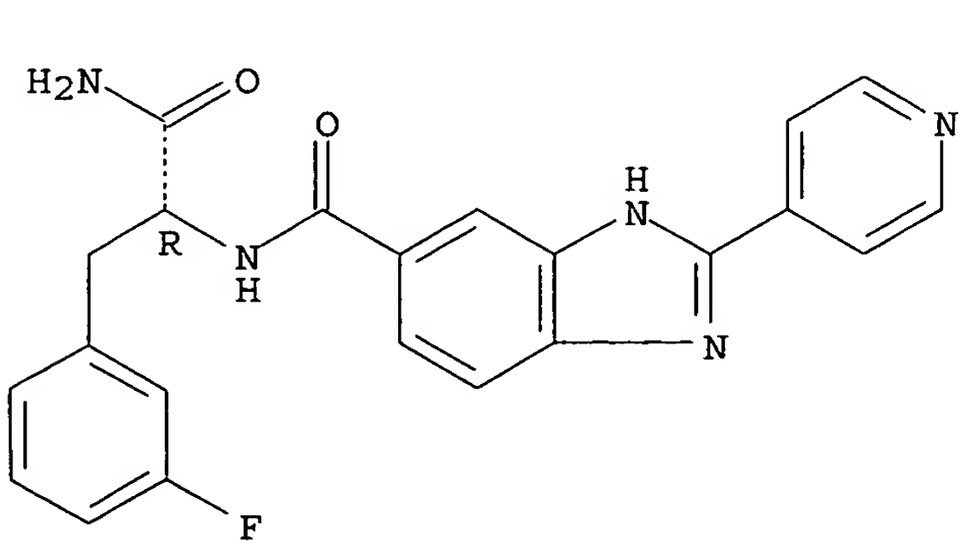
RN 313065-48-4 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-2-amino-2-oxo-1-(phenylmethyl)ethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



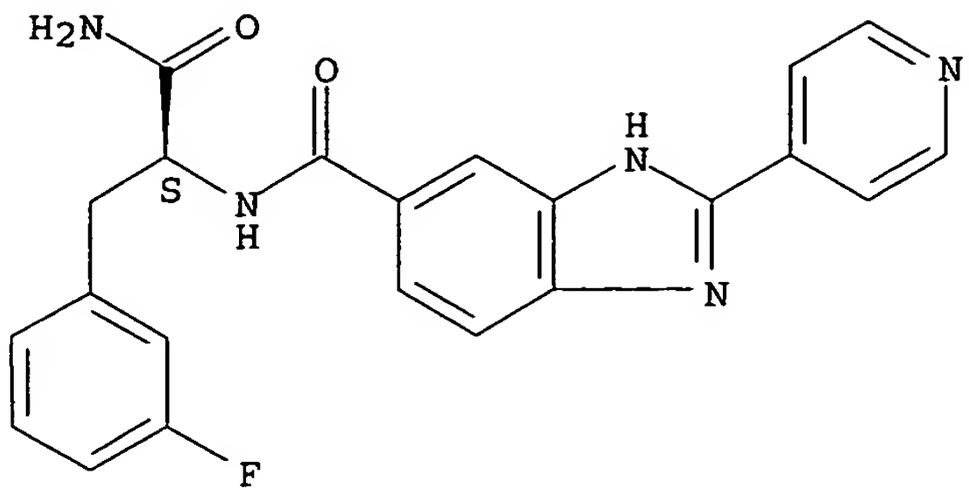
RN 313065-49-5 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1R)-2-amino-1-[(3-fluorophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



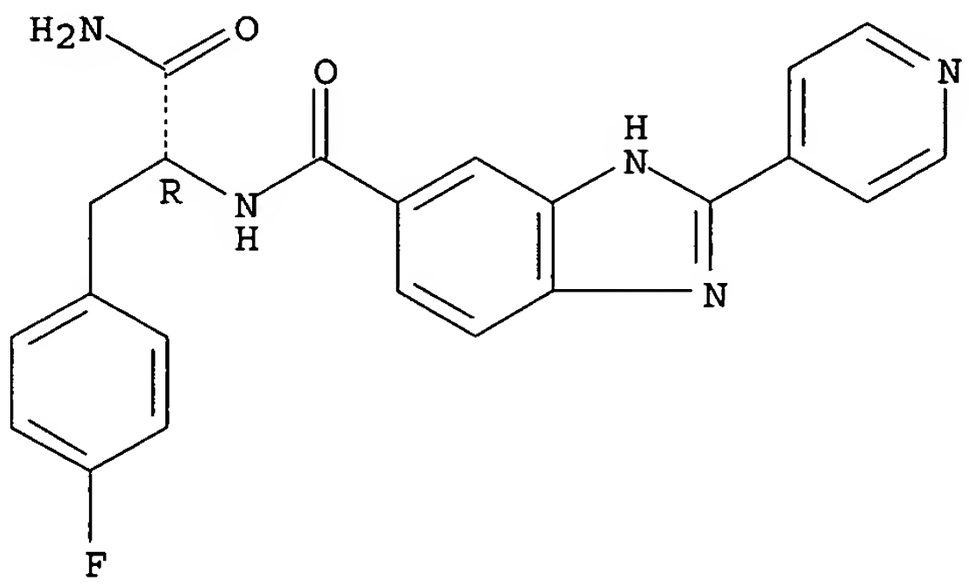
RN 313065-50-8 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-2-amino-1-[(3-fluorophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



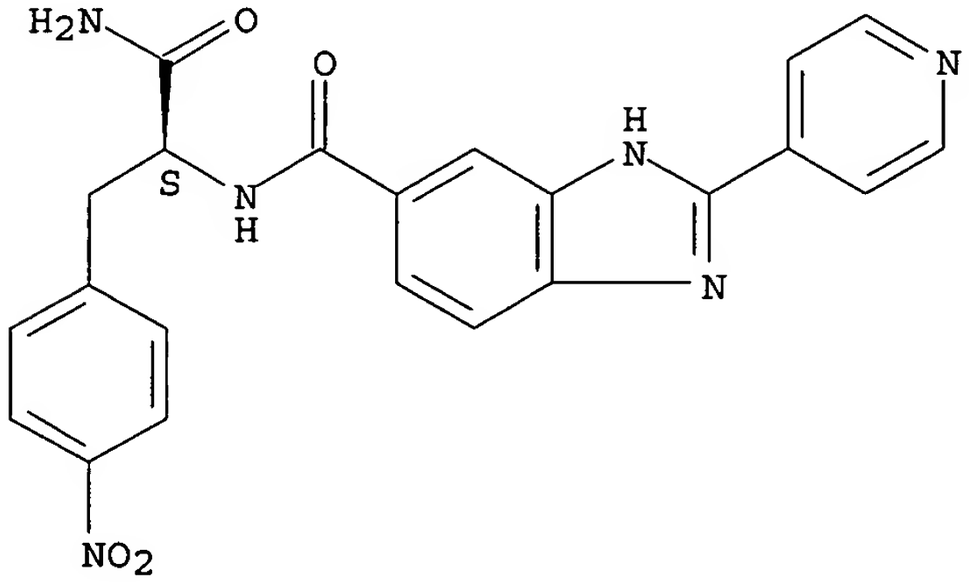
RN 313065-51-9 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1R)-2-amino-1-[(4-fluorophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

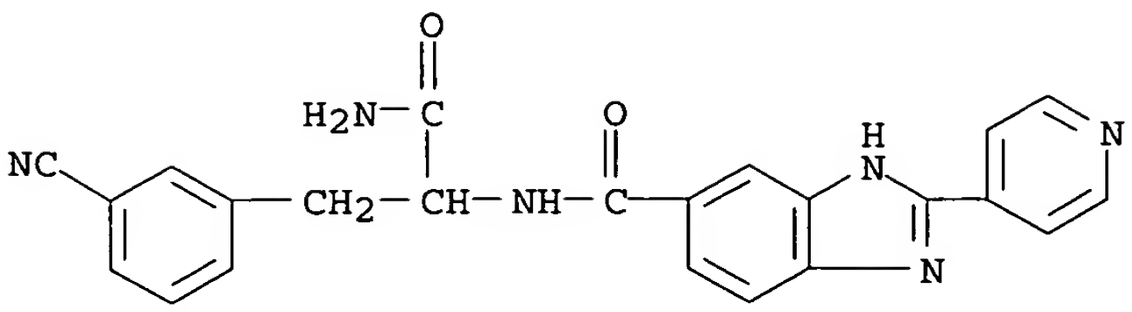


RN 313065-52-0 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-2-amino-1-[(4-nitrophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

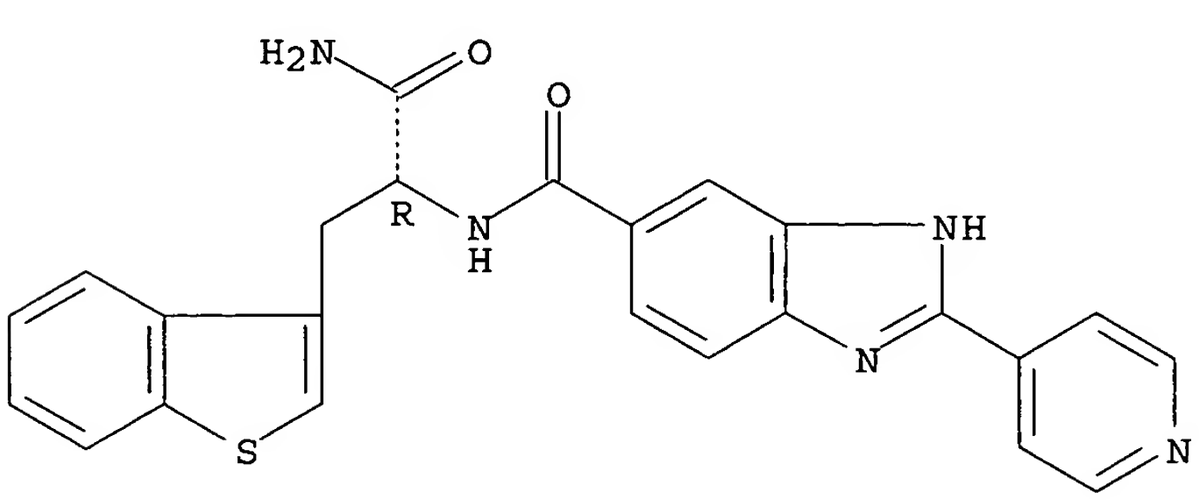


RN 313065-53-1 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[2-amino-1-[(3-cyanophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

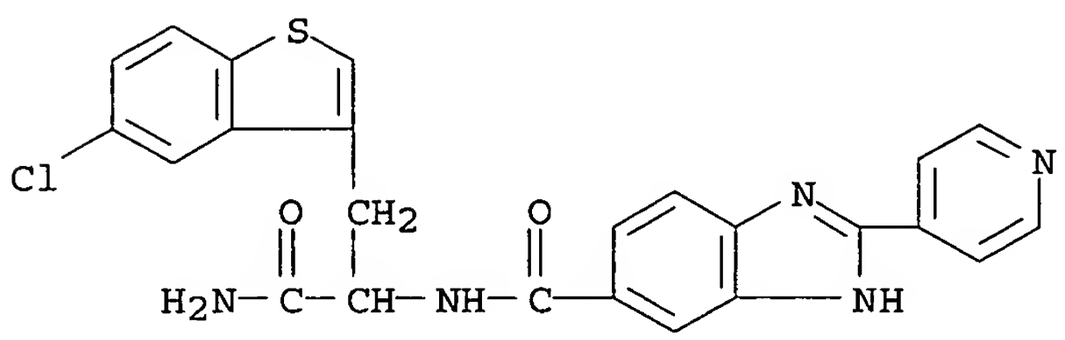


RN 313065-54-2 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1R)-2-amino-1-(benzo[b]thien-3-ylmethyl)-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

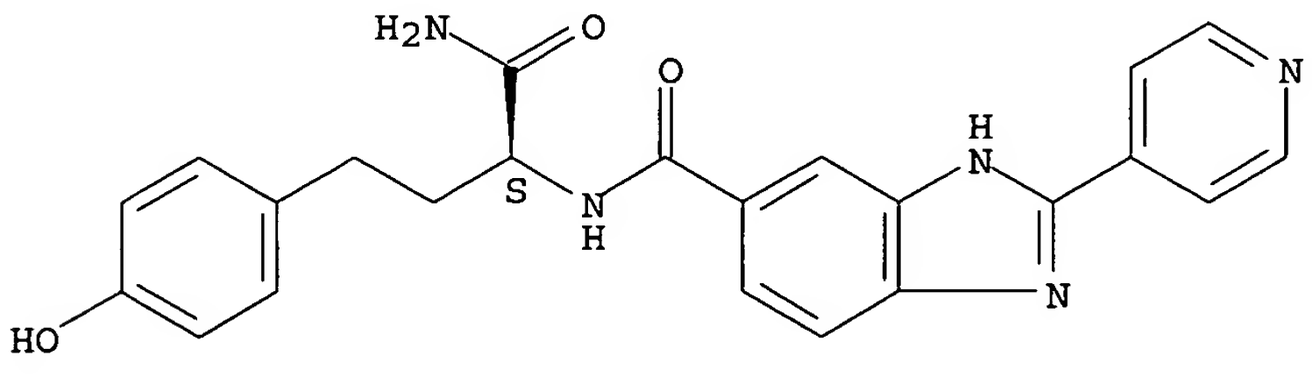


RN 313065-55-3 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[2-amino-1-[(5-chlorobenzo[b]thien-3-yl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)



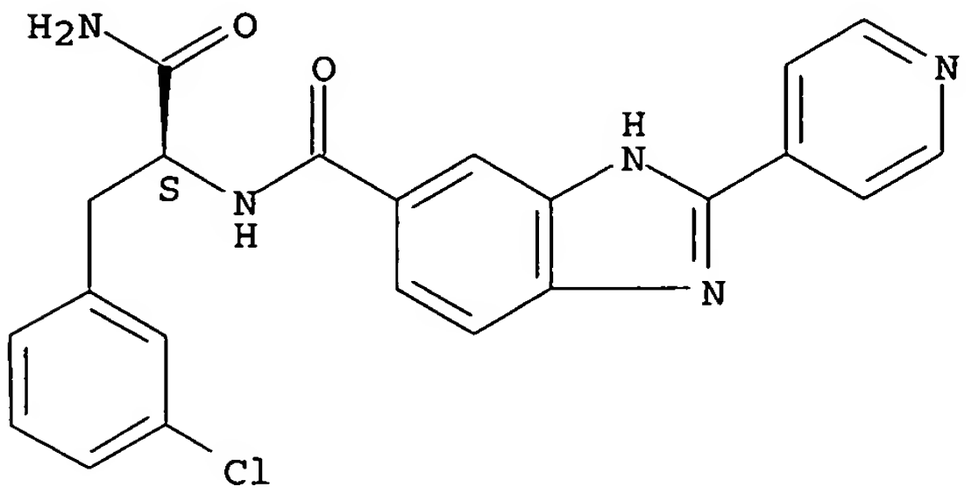
RN 313065-56-4 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-1-(aminocarbonyl)-3-(4-hydroxyphenyl)propyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



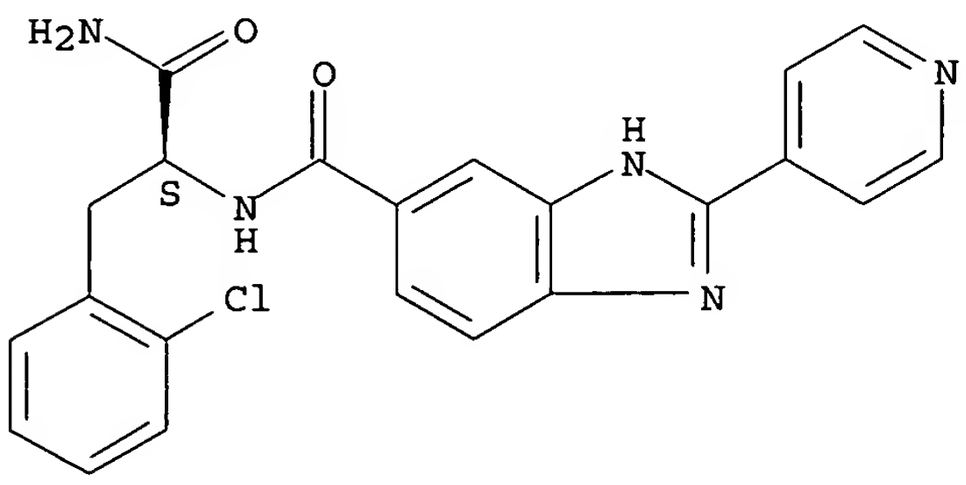
RN 313065-57-5 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-2-amino-1-[(3-chlorophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



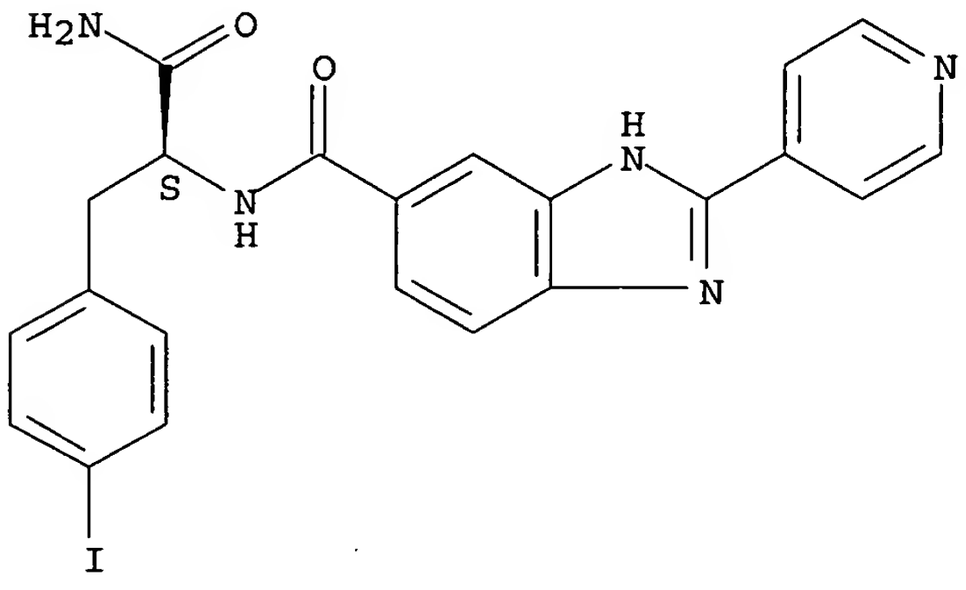
RN 313065-58-6 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-2-amino-1-[(2-chlorophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



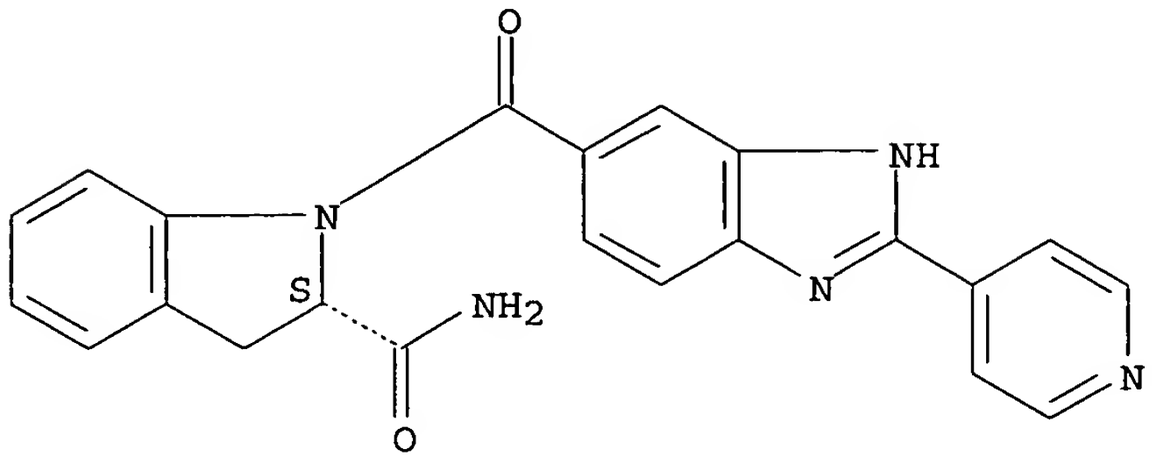
RN 313065-59-7 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-2-amino-1-[(4-iodophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

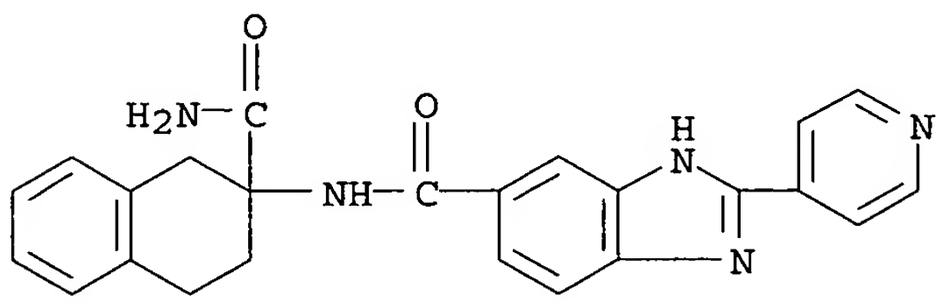


RN 313065-60-0 HCAPLUS
CN 1H-Indole-2-carboxamide, 2,3-dihydro-1-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

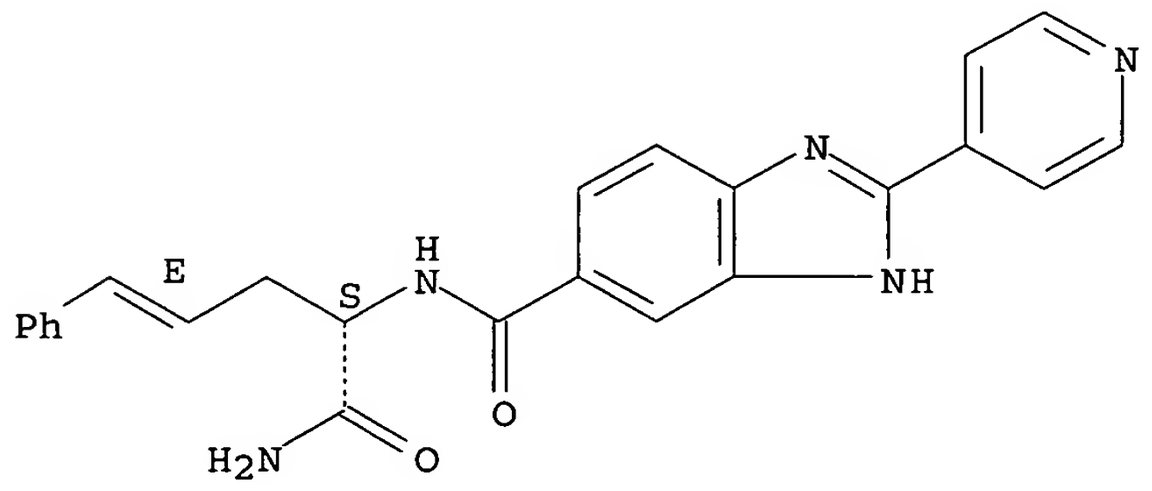


RN 313065-61-1 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[2-(aminocarbonyl)-1,2,3,4-tetrahydro-2-naphthalenyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)



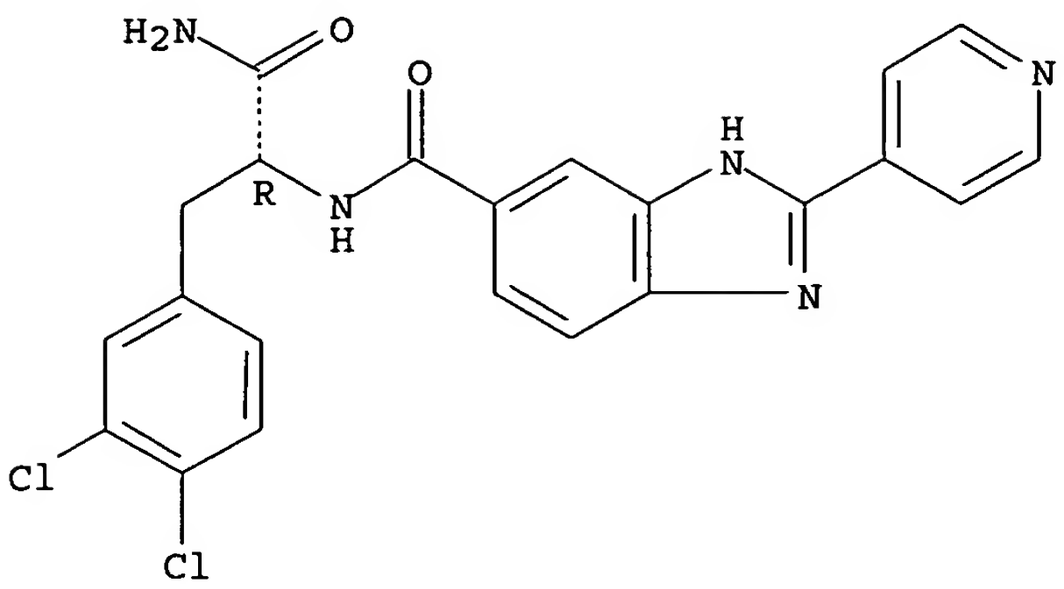
RN 313065-62-2 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S,3E)-1-(aminocarbonyl)-4-phenyl-3-butenyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



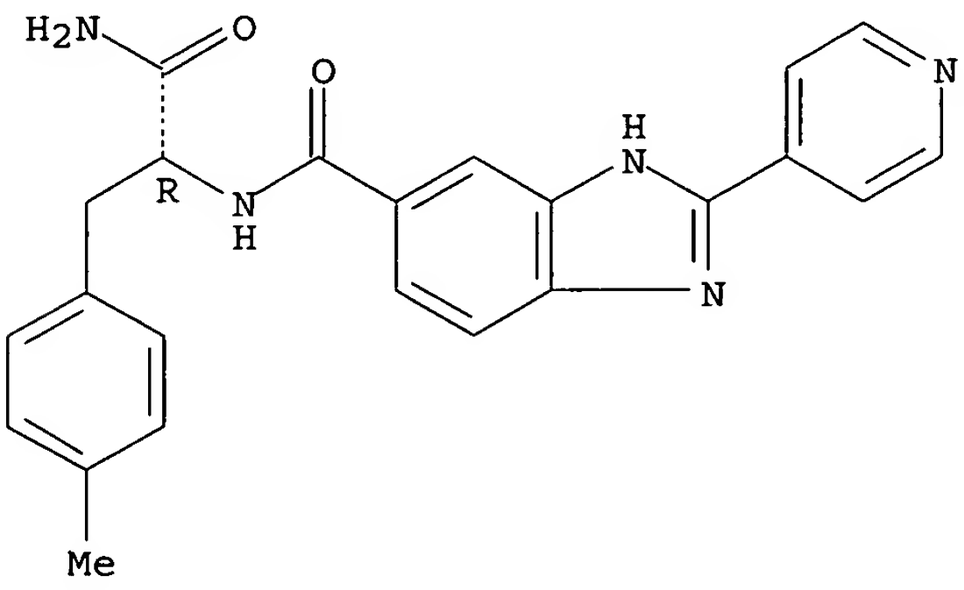
RN 313065-63-3 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1R)-2-amino-1-[(3,4-dichlorophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



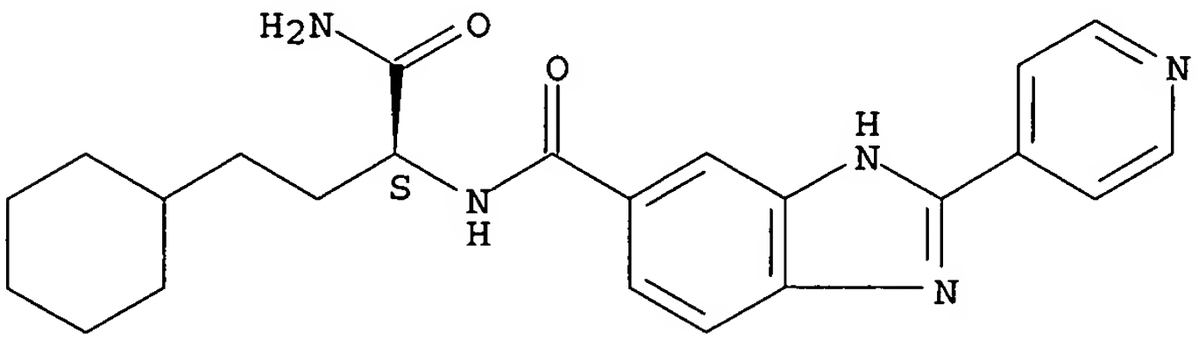
RN 313065-64-4 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1R)-2-amino-1-[(4-methylphenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



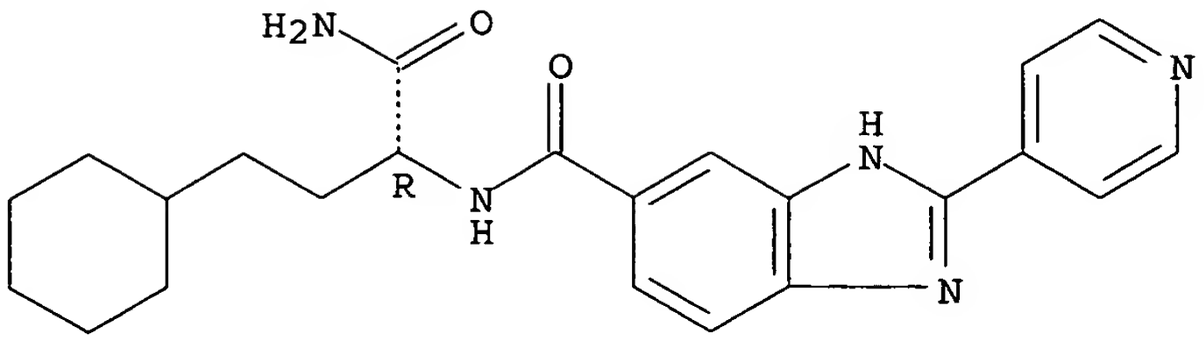
RN 313065-65-5 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-1-(aminocarbonyl)-3-cyclohexylpropyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



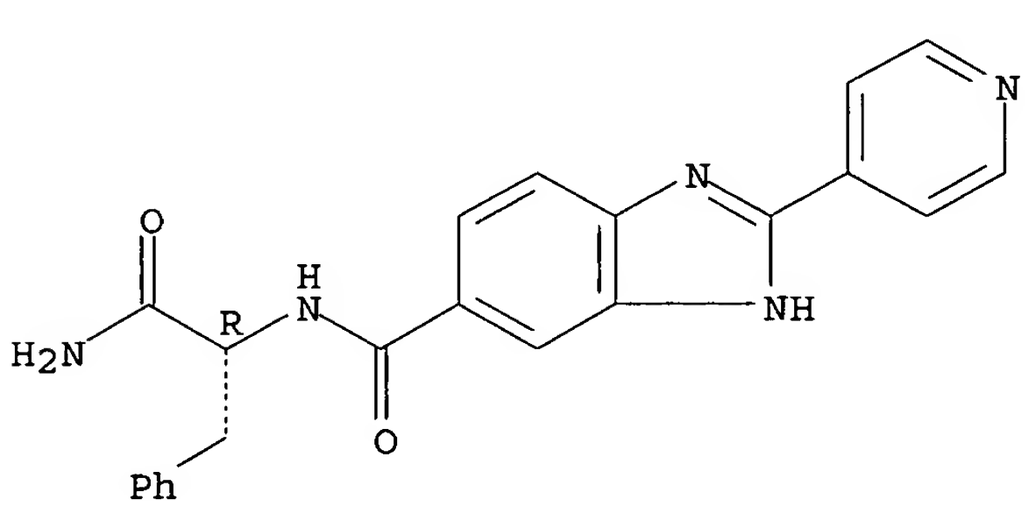
RN 313065-66-6 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1R)-1-(aminocarbonyl)-3-cyclohexylpropyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



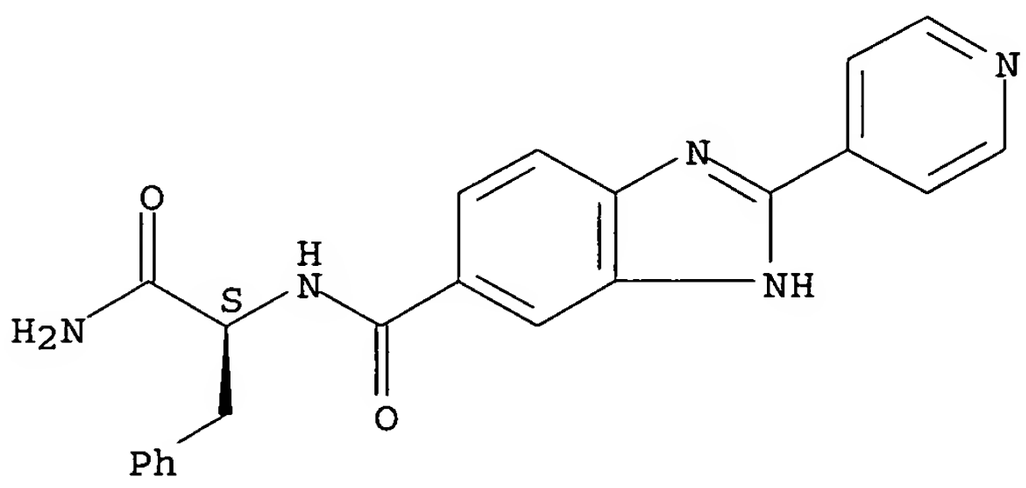
RN 313065-67-7 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1R)-2-amino-2-oxo-1-(phenylmethyl)ethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



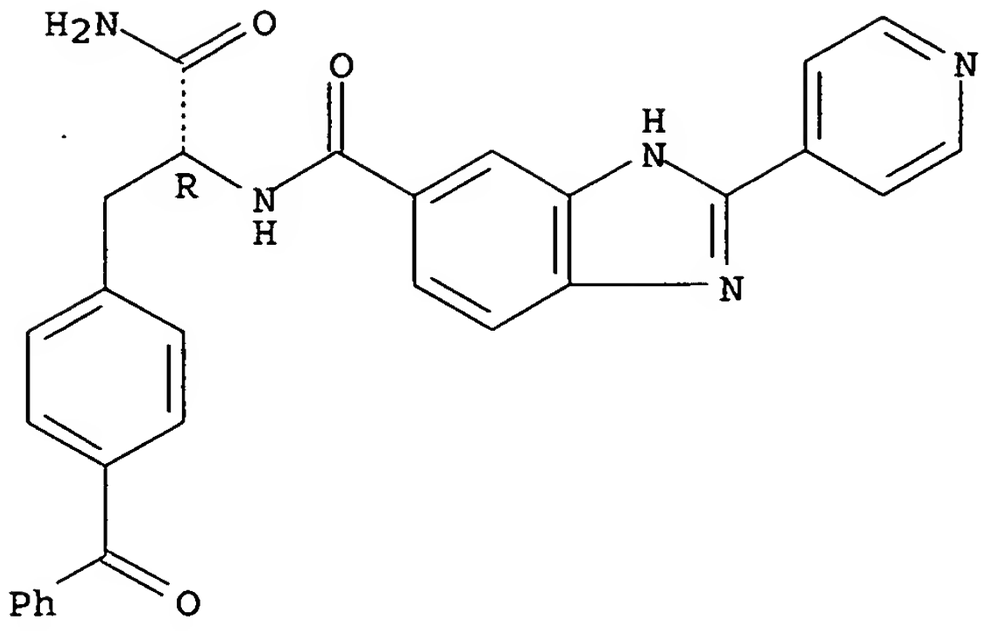
RN 313065-68-8 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-2-amino-2-oxo-1-(phenylmethyl)ethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



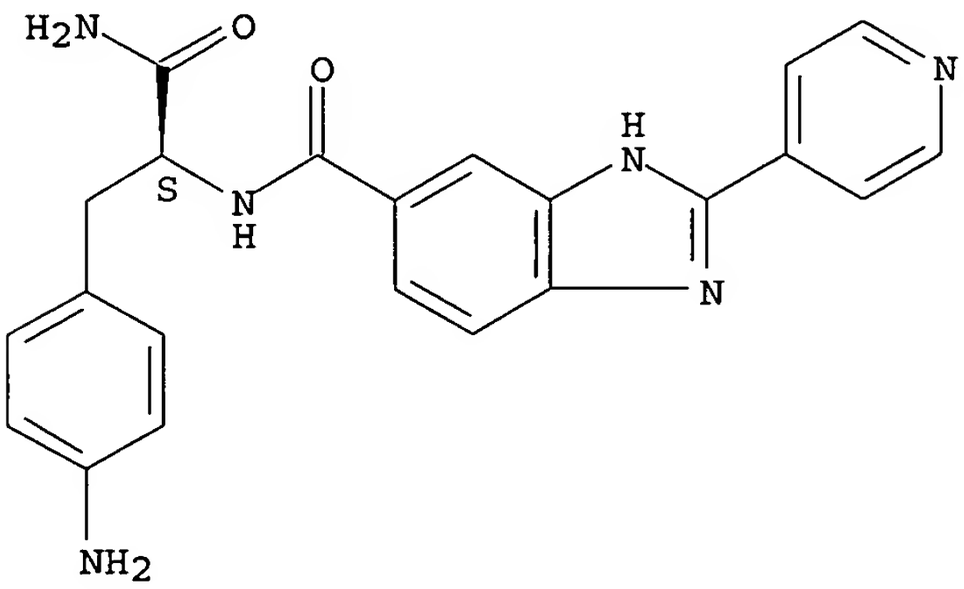
RN 313065-69-9 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1R)-2-amino-1-[(4-benzoylphenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



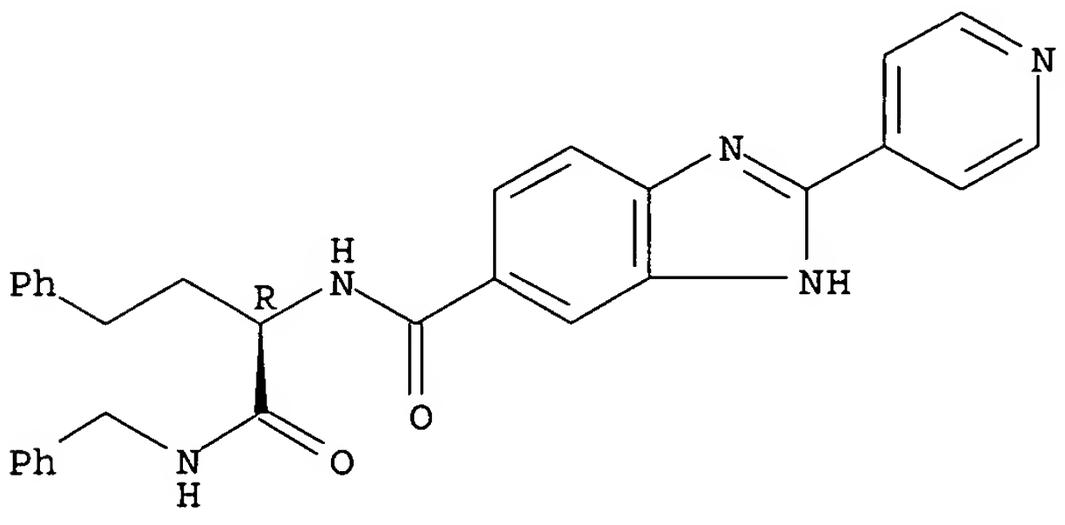
RN 313065-71-3 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-2-amino-1-[(4-aminophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 313065-72-4 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1R)-3-phenyl-1-[[(phenylmethyl)amino]carbonyl]propyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

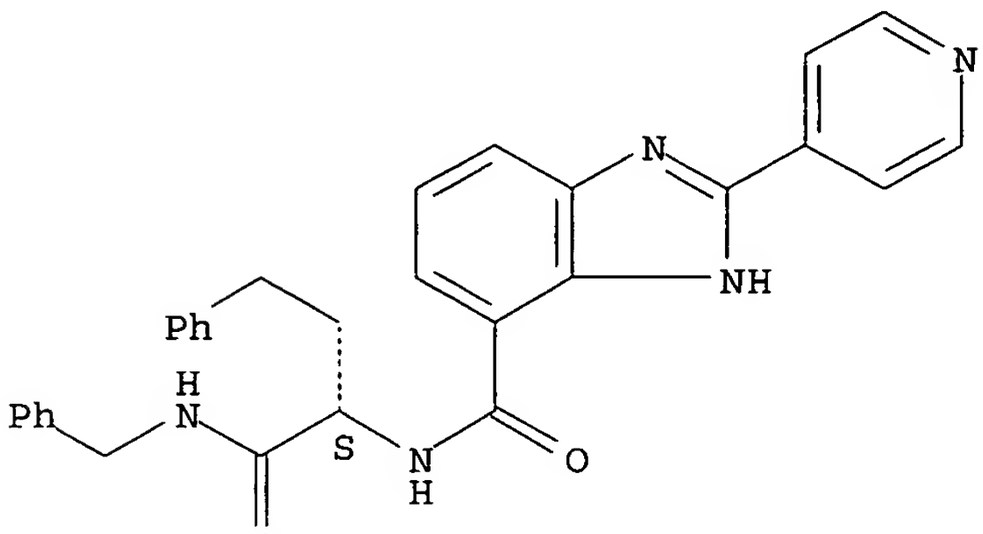
Absolute stereochemistry.



RN 313065-73-5 HCAPLUS

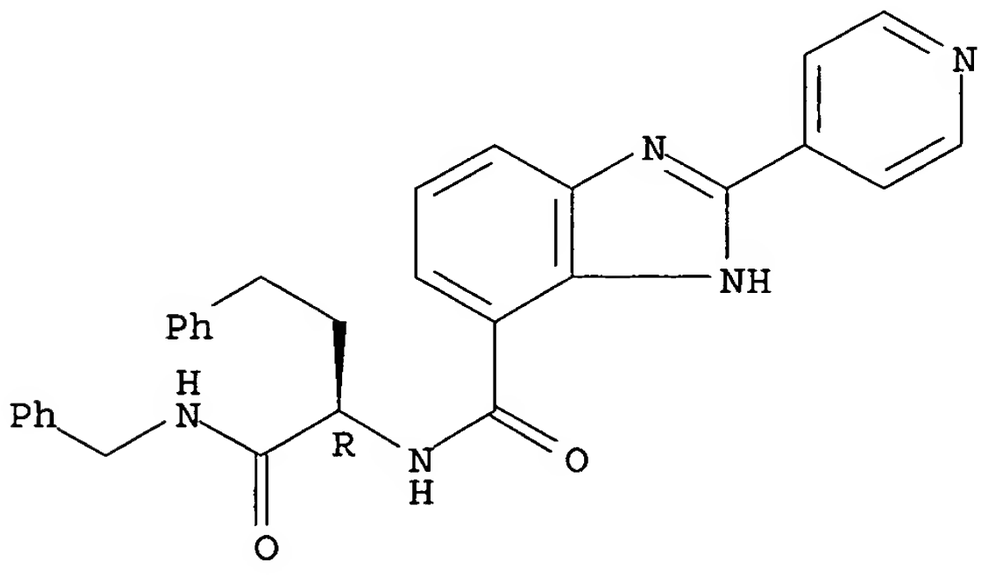
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-3-phenyl-1-[[(phenylmethyl)amino]carbonyl]propyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



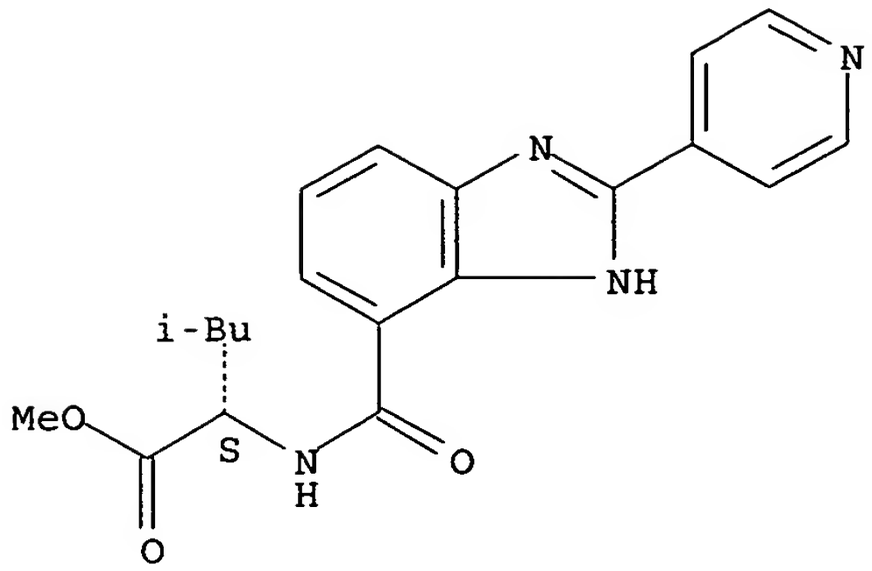
RN 313065-74-6 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1R)-3-phenyl-1-[[(phenylmethyl)amino]carbonyl]propyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



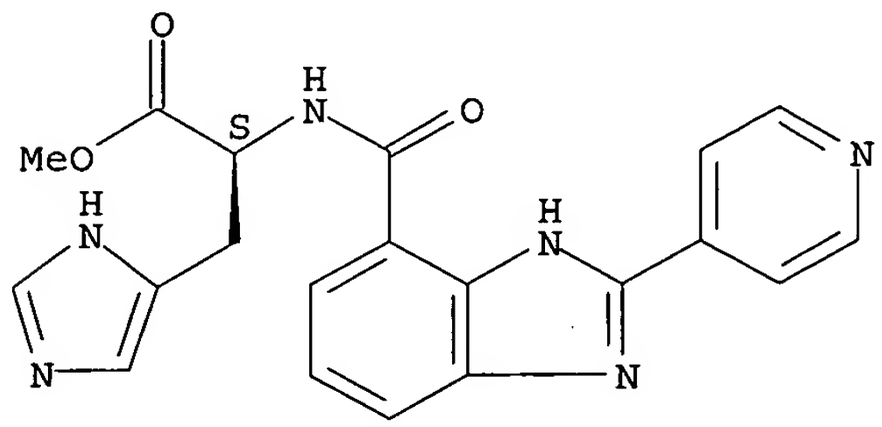
RN 313065-81-5 HCAPLUS
CN L-Leucine, N-[[2-(4-pyridinyl)-1H-benzimidazol-4-yl]carbonyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



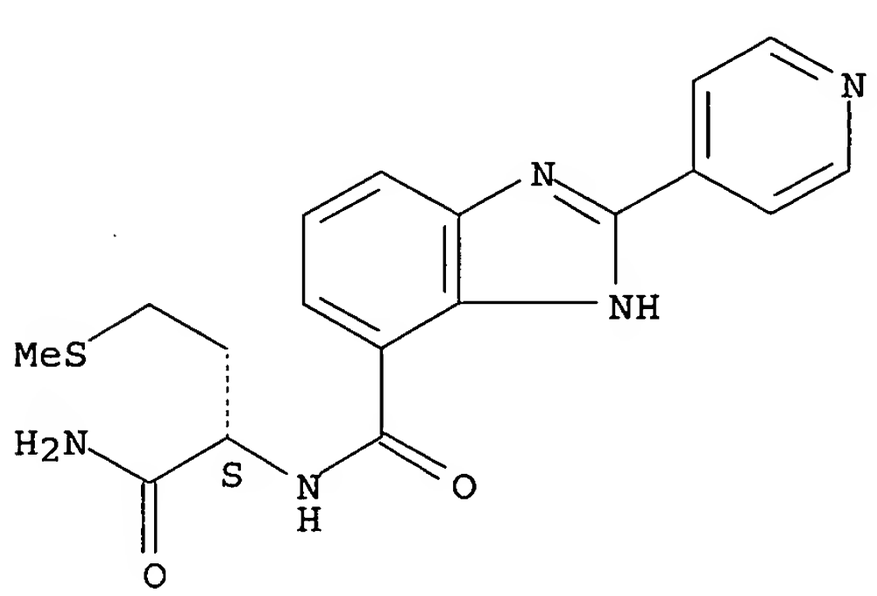
RN 313065-88-2 HCAPLUS
CN L-Histidine, N-[[2-(4-pyridinyl)-1H-benzimidazol-4-yl]carbonyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



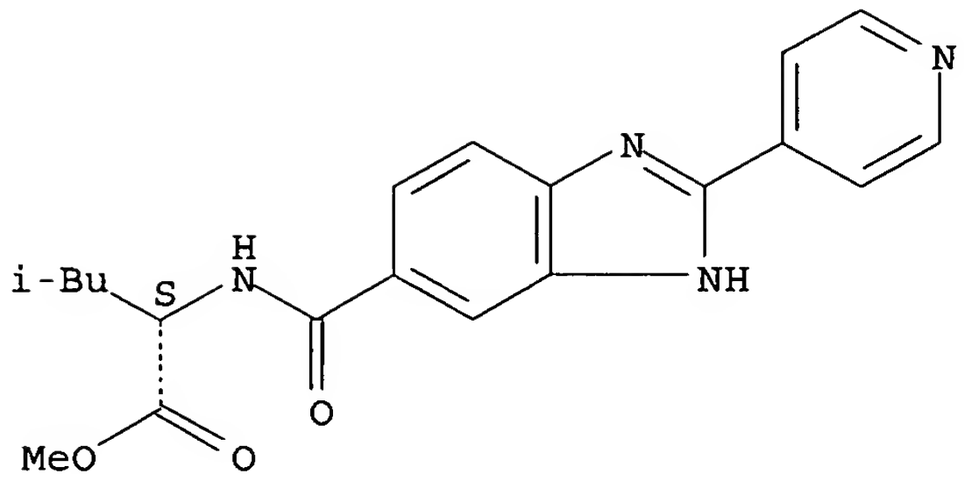
RN 313065-90-6 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-1-(aminocarbonyl)-3-(methylthio)propyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



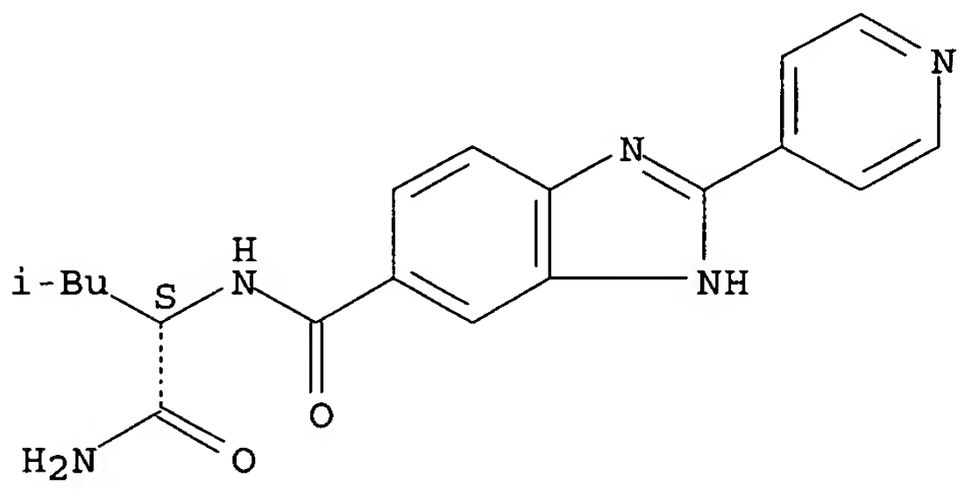
RN 313065-92-8 HCAPLUS
CN L-Leucine, N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



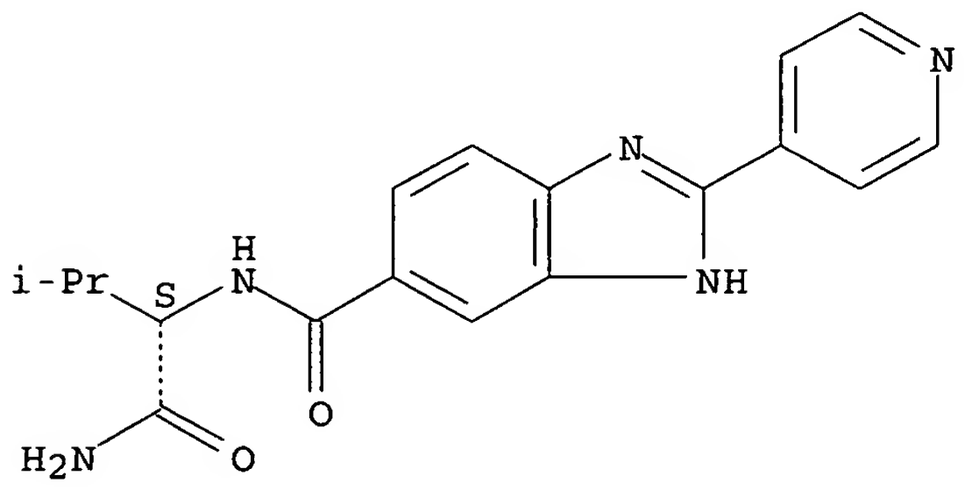
RN 313065-93-9 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-1-(aminocarbonyl)-3-methylbutyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

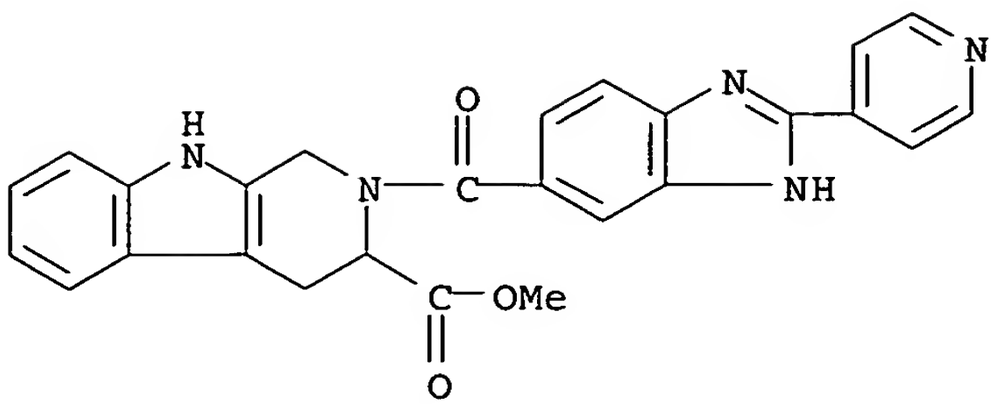


RN 313065-94-0 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

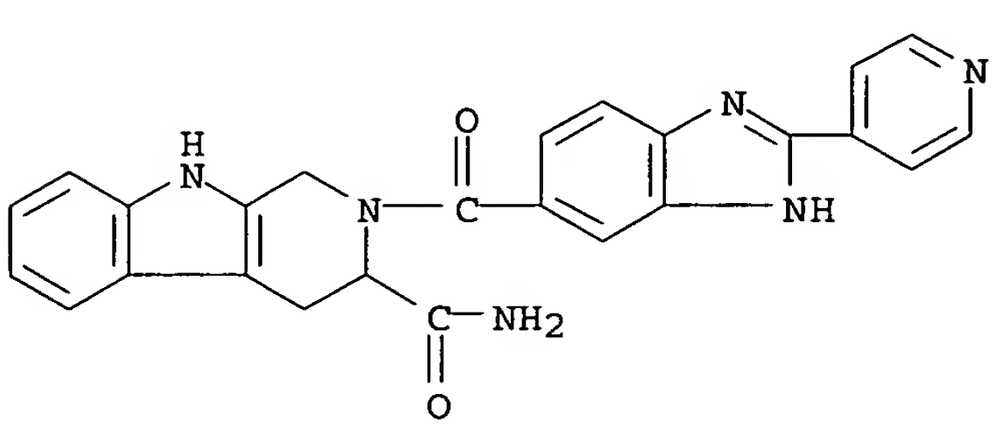
Absolute stereochemistry.



RN 313065-95-1 HCAPLUS
CN 1H-Pyrido[3,4-b]indole-3-carboxylic acid, 2,3,4,9-tetrahydro-2-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]-, methyl ester (9CI) (CA INDEX NAME)

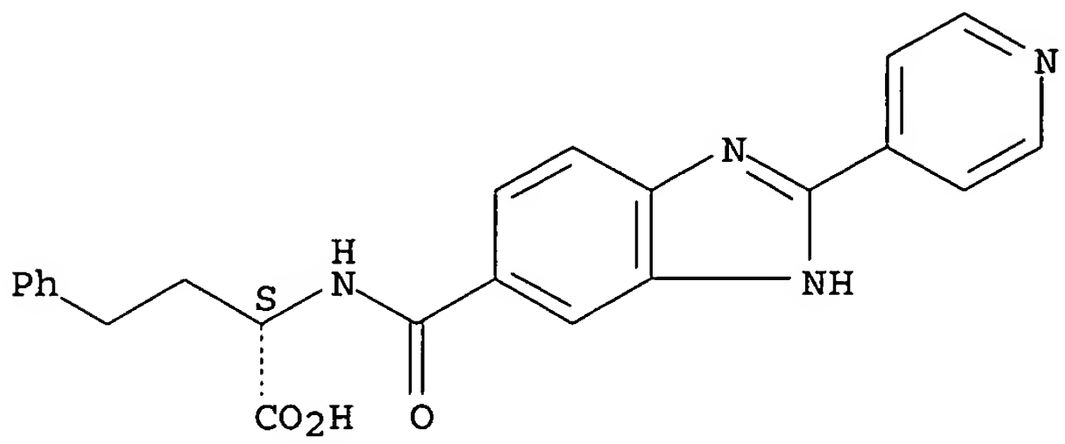


RN 313065-96-2 HCAPLUS
CN 1H-Pyrido[3,4-b]indole-3-carboxamide, 2,3,4,9-tetrahydro-2-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]- (9CI) (CA INDEX NAME)



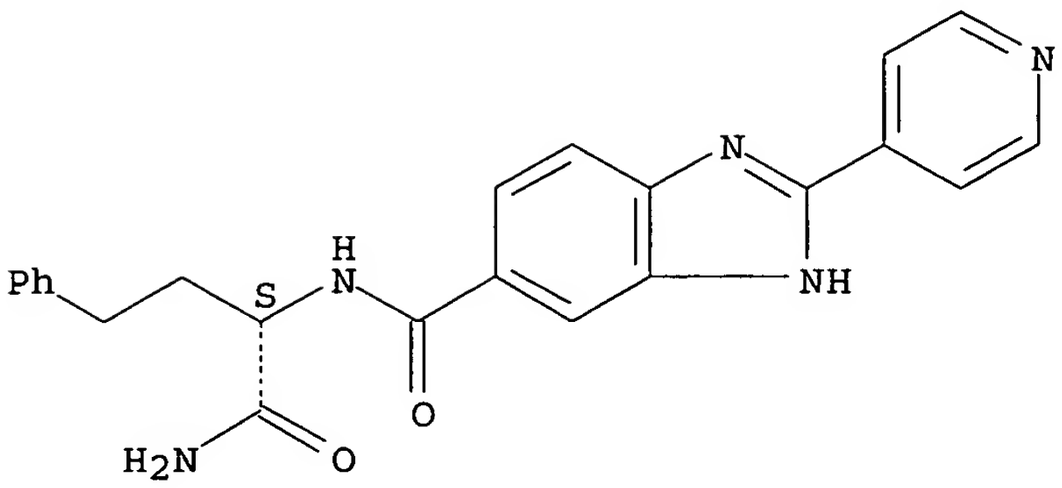
RN 313065-98-4 HCAPLUS
CN Benzenebutanoic acid, α-[[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]amino]-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



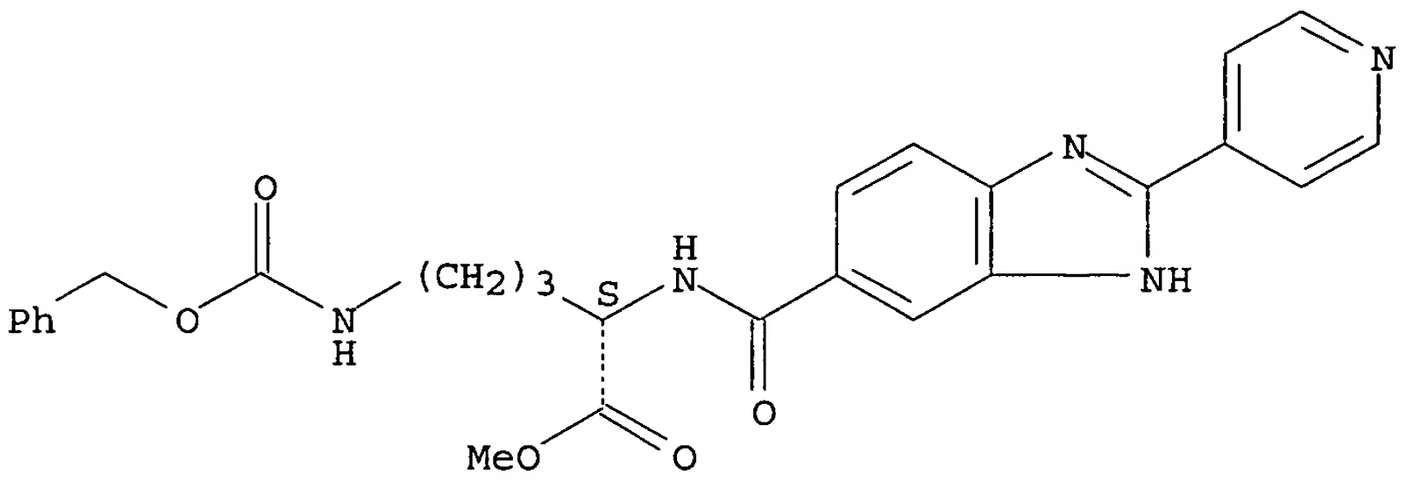
RN 313065-99-5 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-1-(aminocarbonyl)-3-phenylpropyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



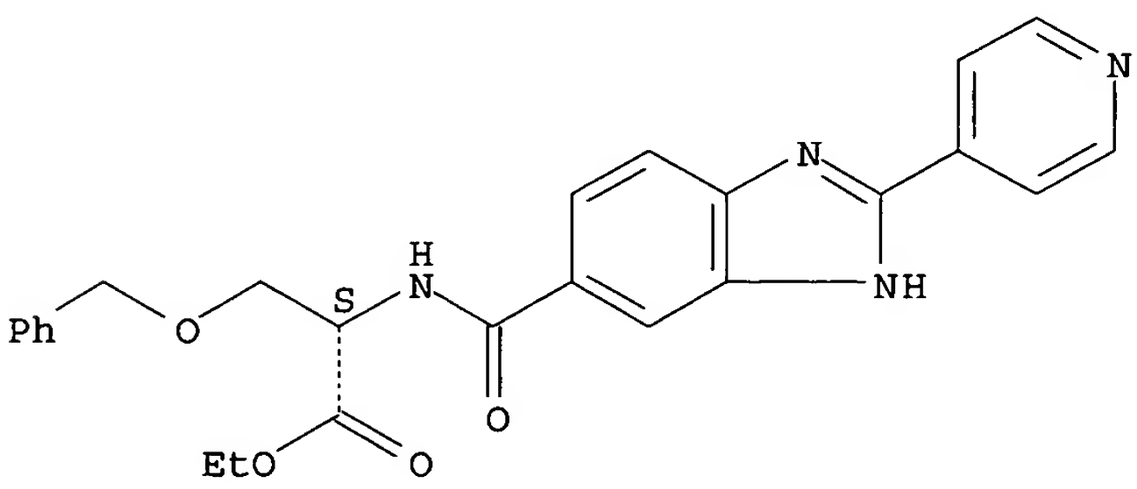
RN 313066-00-1 HCAPLUS
CN L-Ornithine, N5-[(phenylmethoxy)carbonyl]-N2-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



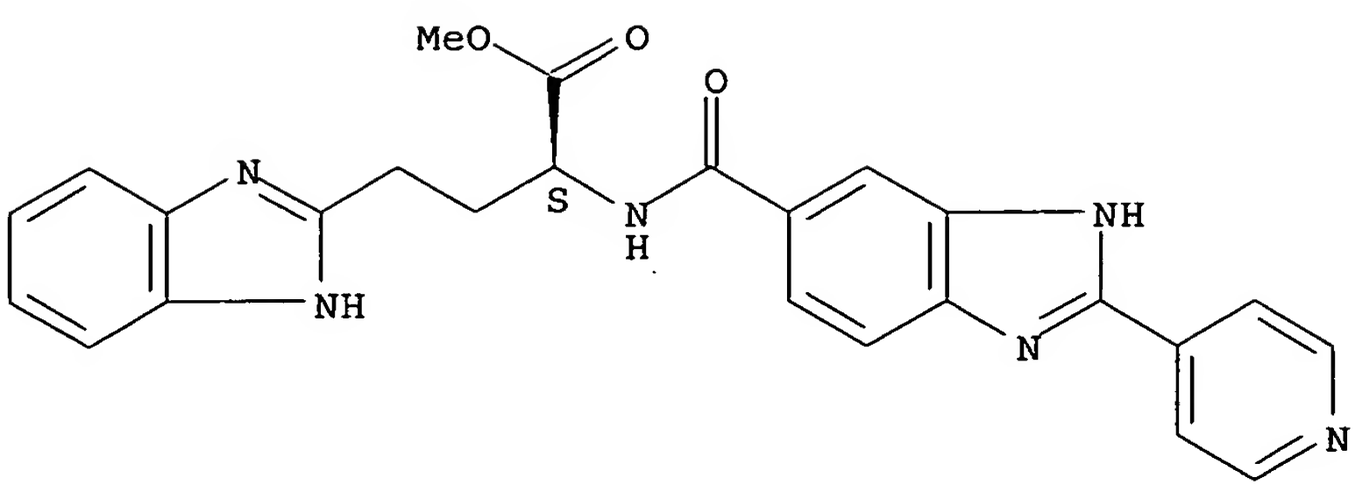
RN 313066-01-2 HCAPLUS
CN L-Serine, O-(phenylmethyl)-N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



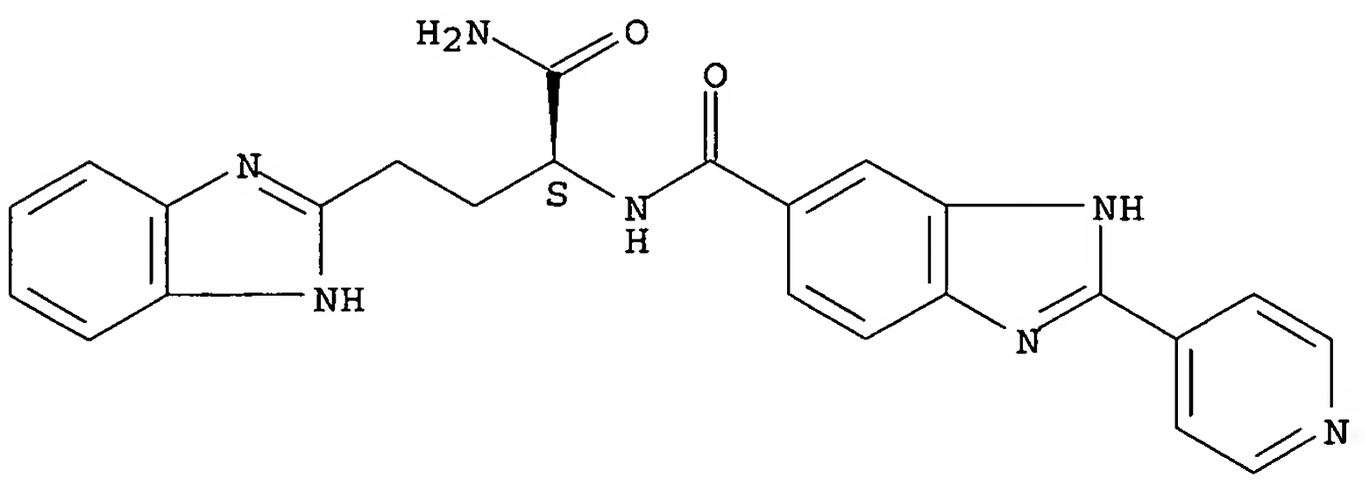
RN 313066-02-3 HCAPLUS
CN 1H-Benzimidazole-2-butanoic acid, α-[[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]amino]-, methyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



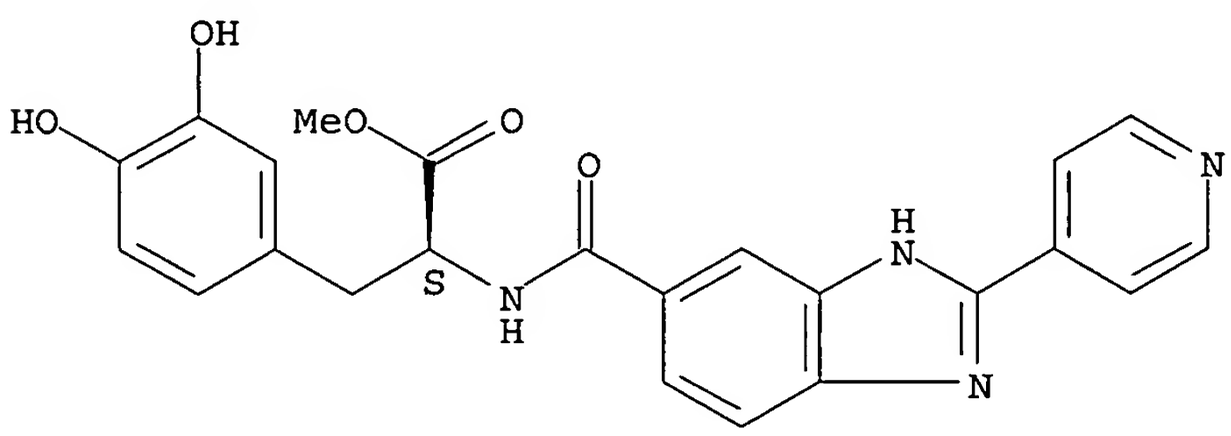
RN 313066-03-4 HCAPLUS
CN 1H-Benzimidazole-2-butanamide, α-[[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]amino]-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



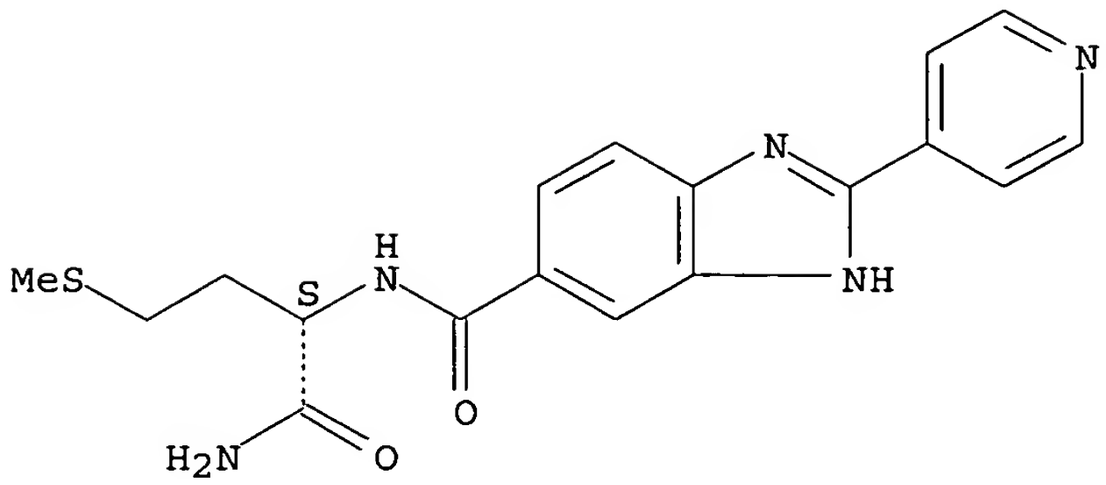
RN 313066-05-6 HCAPLUS
CN L-Tyrosine, 3-hydroxy-N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



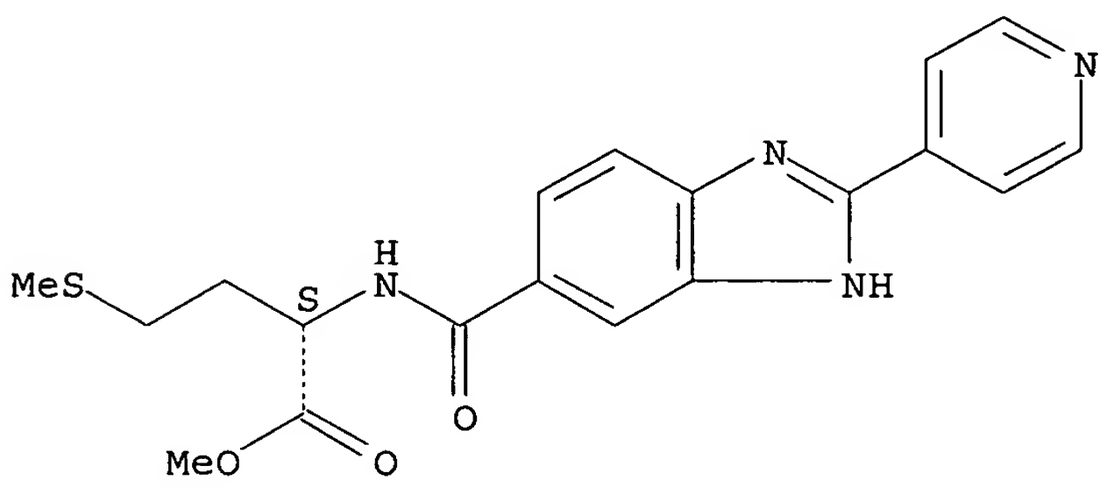
RN 313066-07-8 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-1-(aminocarbonyl)-3-(methylthio)propyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



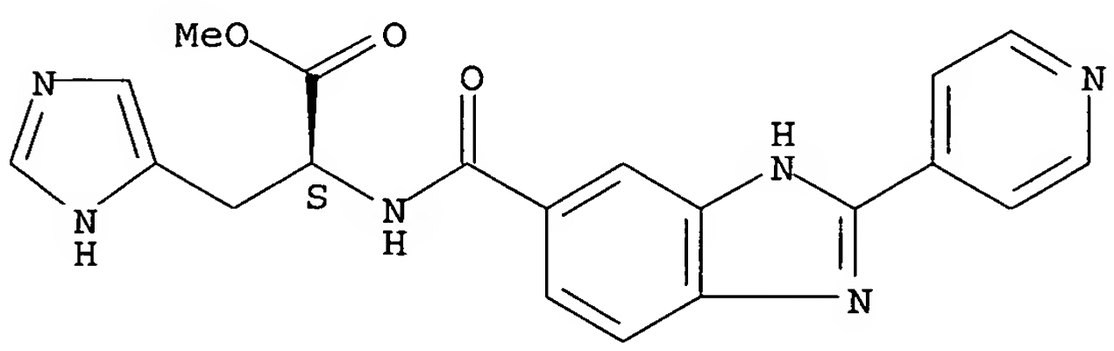
RN 313066-09-0 HCAPLUS
CN L-Methionine, N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



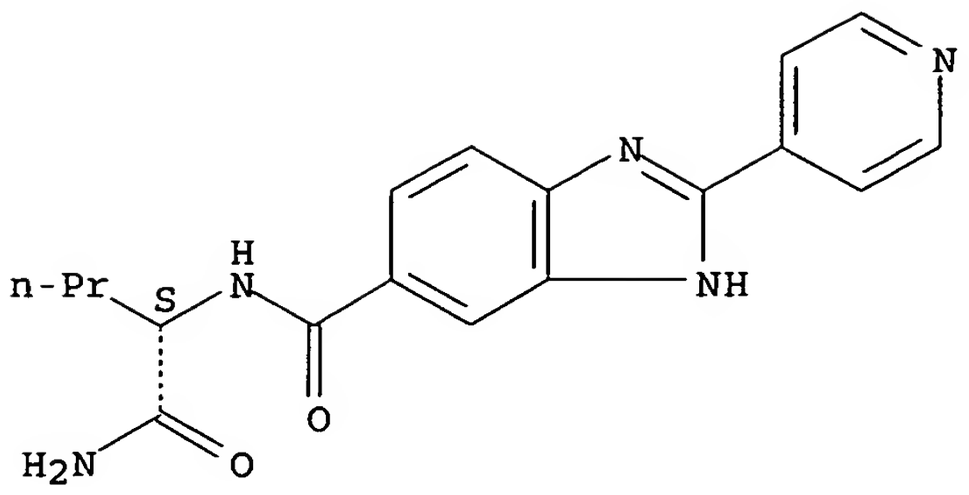
RN 313066-10-3 HCAPLUS
CN L-Histidine, N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



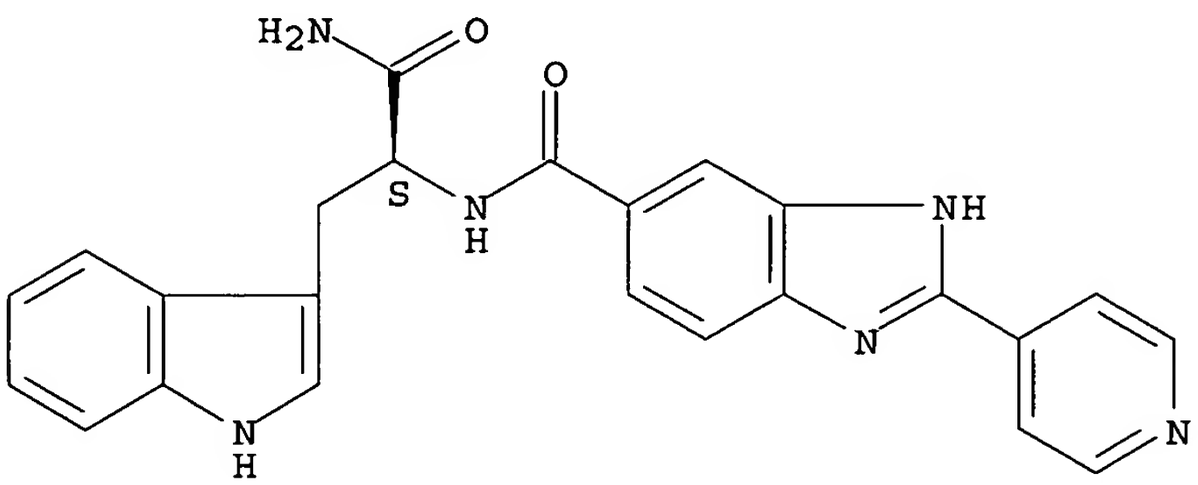
RN 313066-11-4 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-1-(aminocarbonyl)butyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

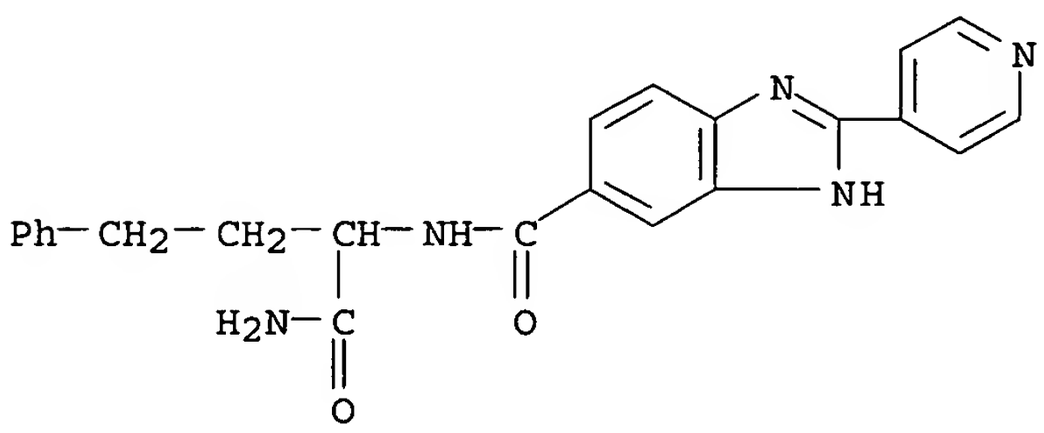


RN 313066-12-5 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-2-amino-1-(1H-indol-3-ylmethyl)-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

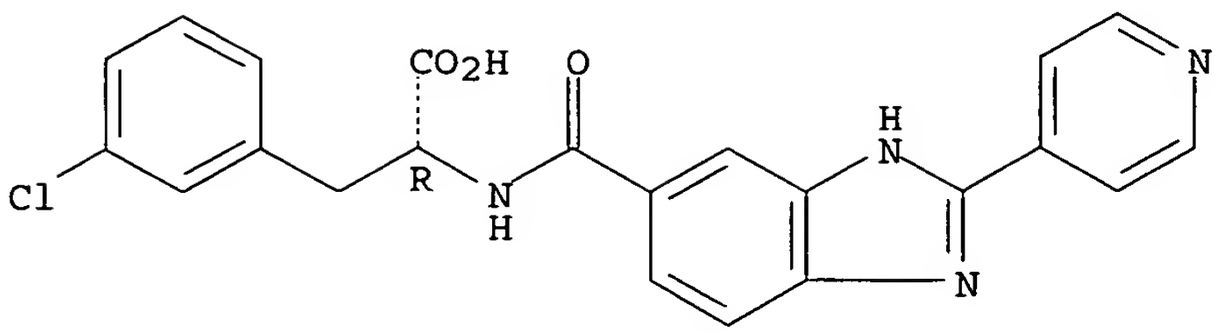


RN 313066-15-8 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[1-(aminocarbonyl)-3-phenylpropyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)



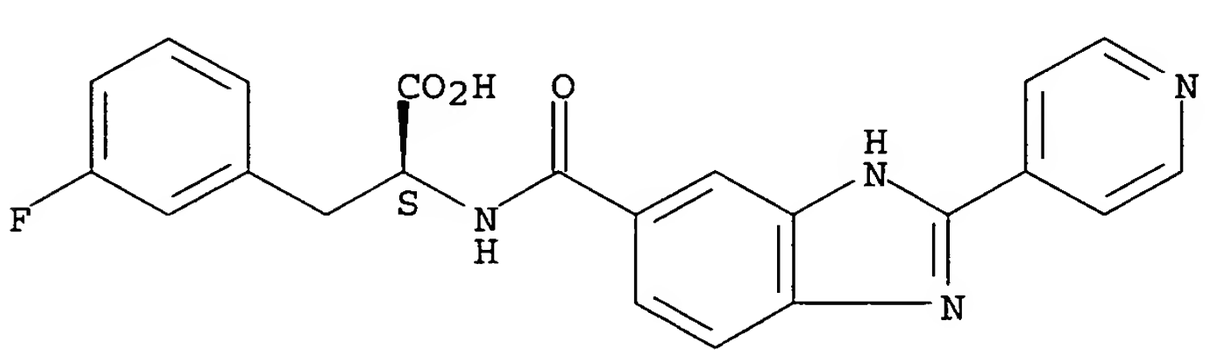
RN 316832-35-6 HCAPLUS
CN D-Phenylalanine, 3-chloro-N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



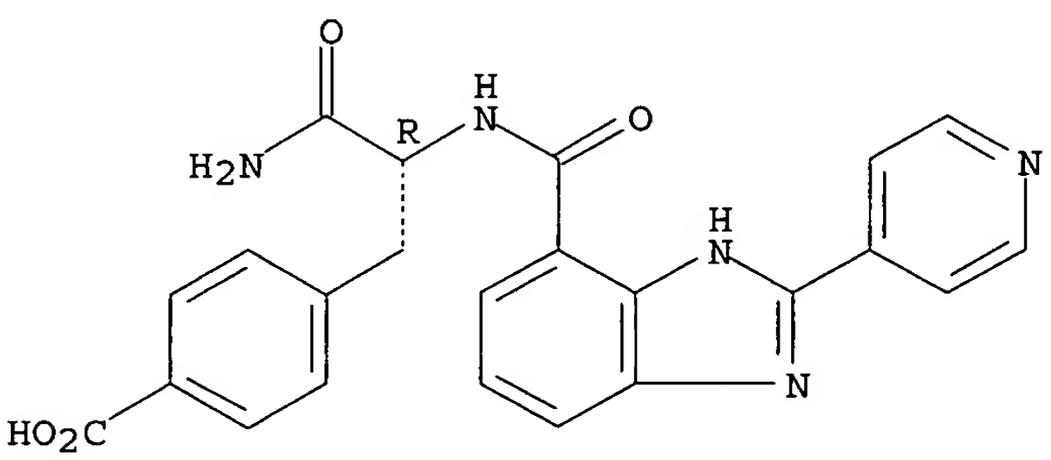
RN 316832-36-7 HCAPLUS
CN L-Phenylalanine, 3-fluoro-N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



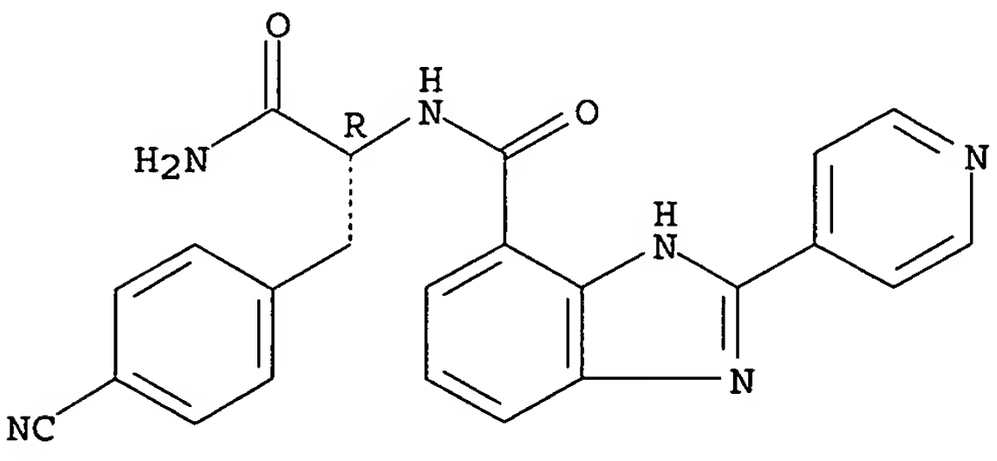
RN 316832-37-8 HCAPLUS
CN Benzoic acid, 4-[(2R)-3-amino-3-oxo-2-[[[2-(4-pyridinyl)-1H-benzimidazol-4-yl]carbonyl]amino]propyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



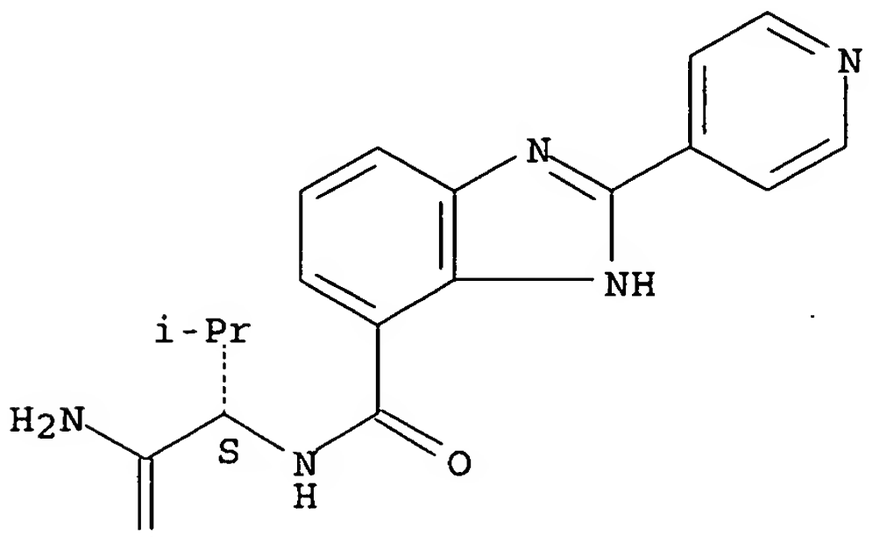
RN 316832-38-9 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1R)-2-amino-1-[(4-cyanophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

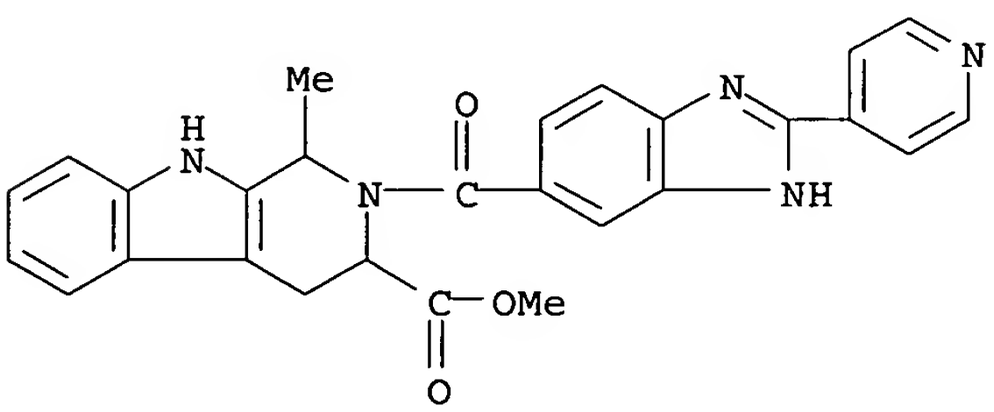


RN 316832-39-0 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

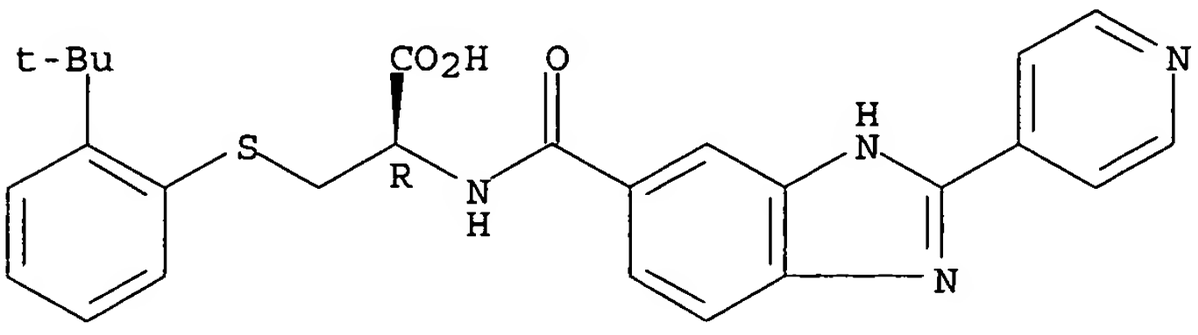


RN 316832-40-3 HCAPLUS
CN 1H-Pyrido[3,4-b]indole-3-carboxylic acid, 2,3,4,9-tetrahydro-1-methyl-2-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]-, methyl ester (9CI) (CA INDEX NAME)



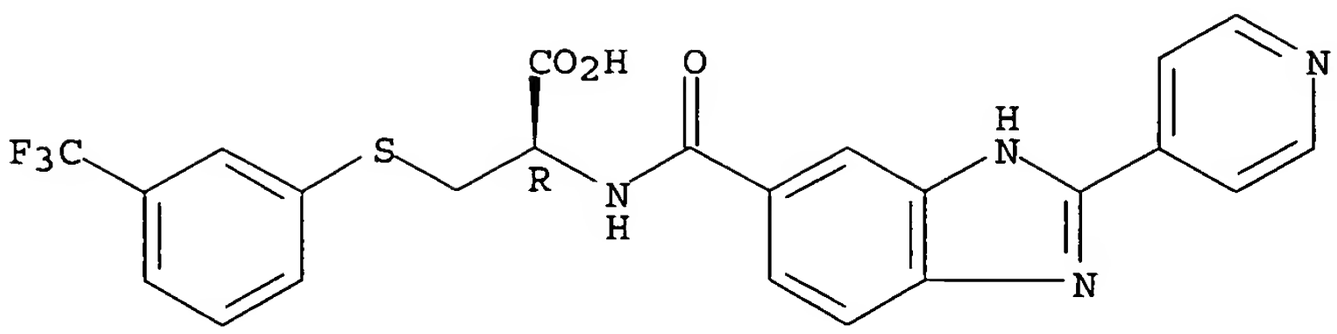
RN 316832-41-4 HCAPLUS
CN L-Cysteine, S-[2-(1,1-dimethylethyl)phenyl]-N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



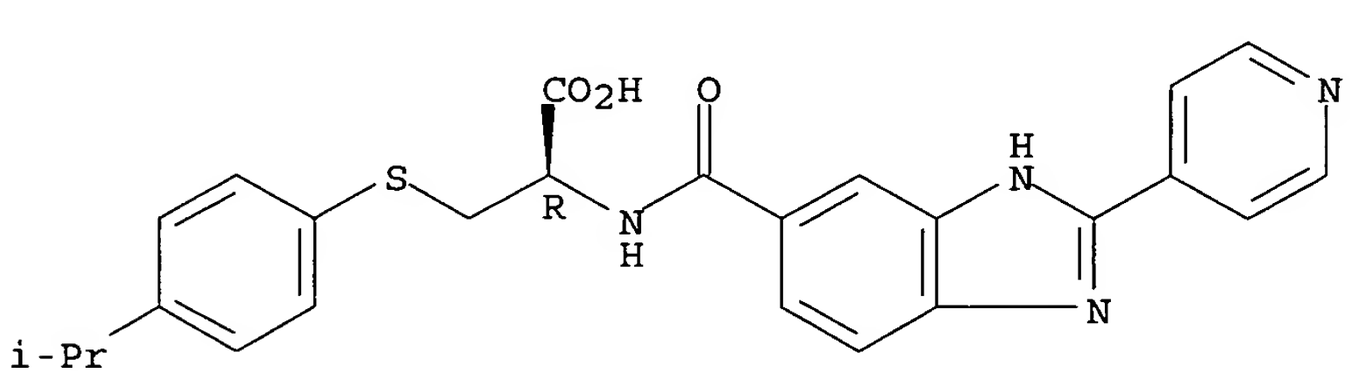
RN 316832-42-5 HCAPLUS
CN L-Cysteine, N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]-S-[3-(trifluoromethyl)phenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



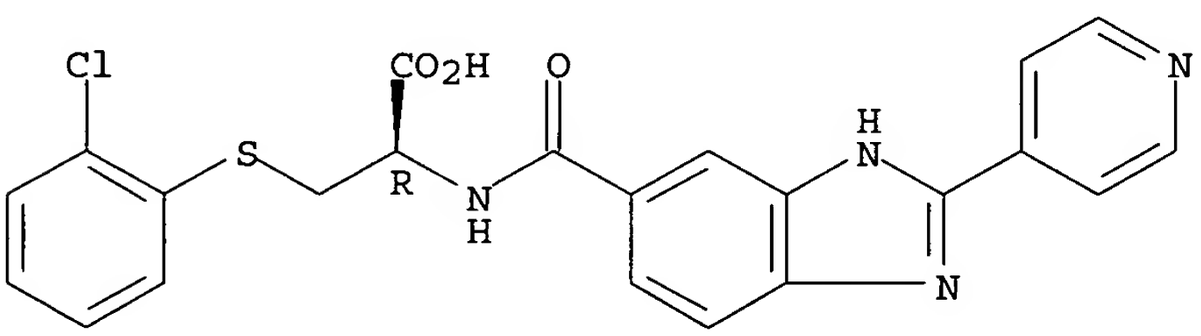
RN 316832-43-6 HCAPLUS
CN L-Cysteine, S-[4-(1-methylethyl)phenyl]-N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



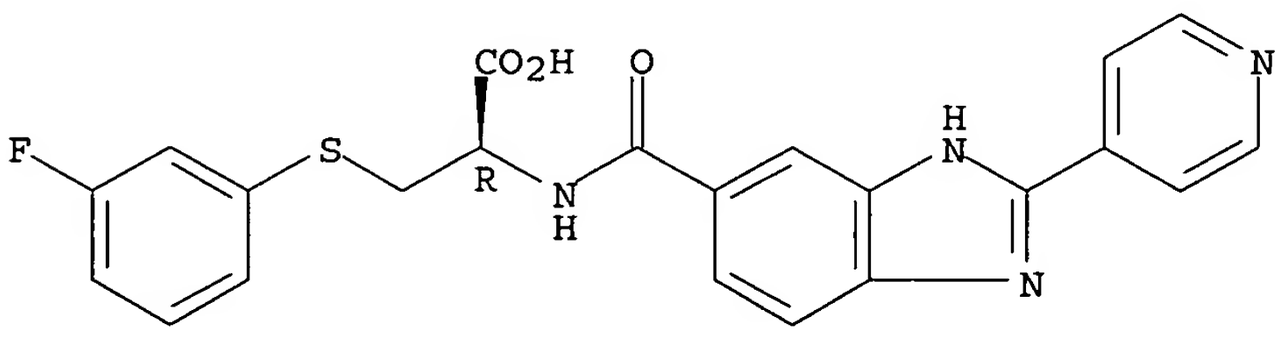
RN 316832-44-7 HCAPLUS
CN L-Cysteine, S-(2-chlorophenyl)-N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



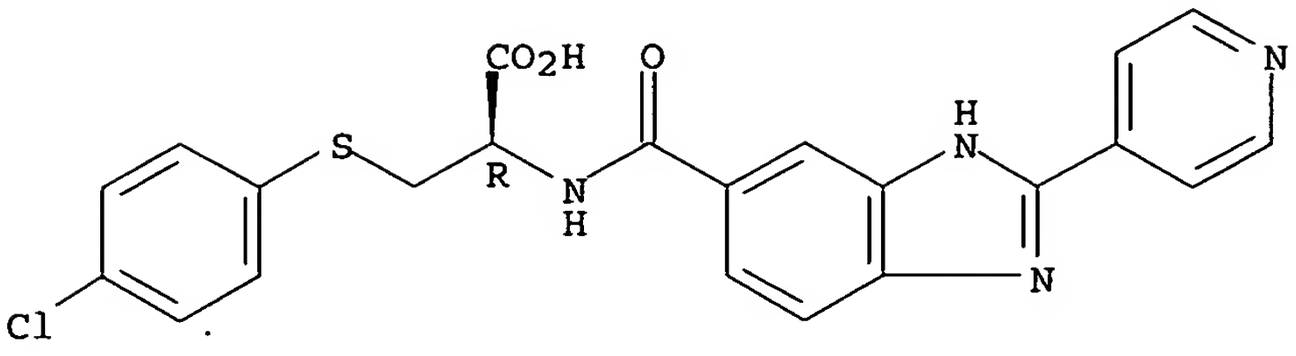
RN 316832-45-8 HCAPLUS
CN L-Cysteine, S-(3-fluorophenyl)-N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



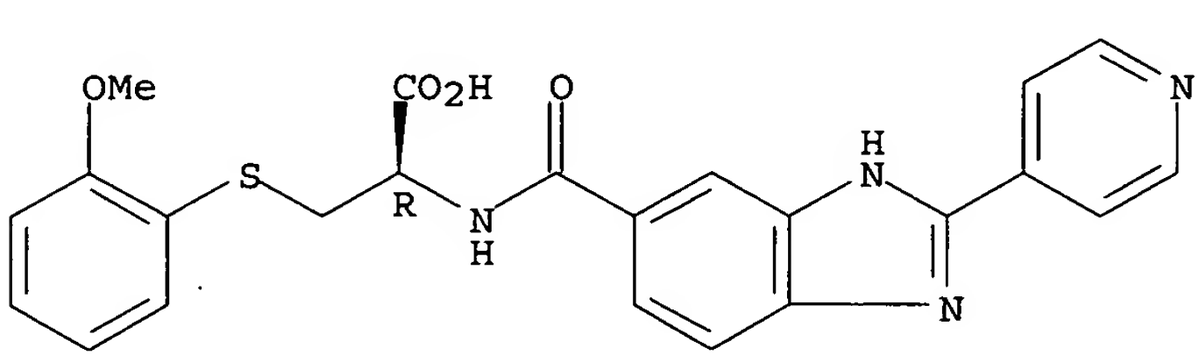
RN 316832-46-9 HCAPLUS
CN L-Cysteine, S-(4-chlorophenyl)-N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



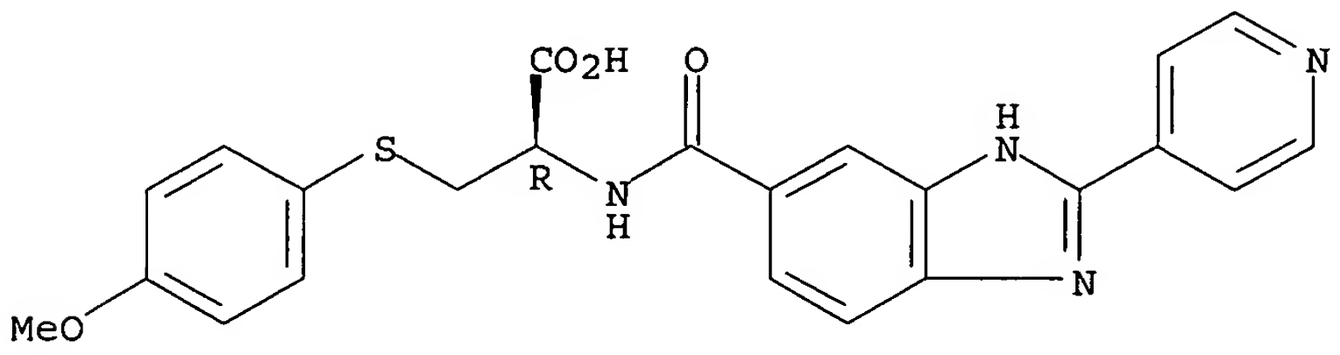
RN 316832-47-0 HCAPLUS
CN L-Cysteine, S-(2-methoxyphenyl)-N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



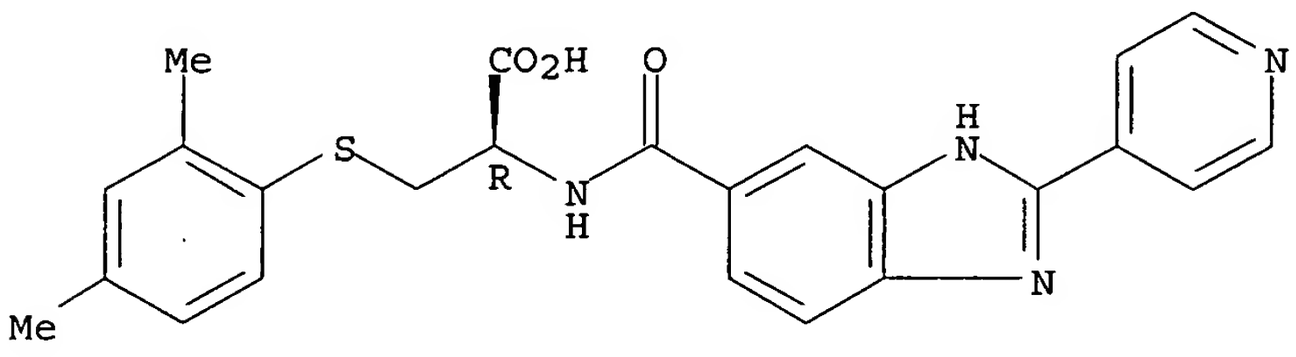
RN 316832-48-1 HCAPLUS
CN L-Cysteine, S-(4-methoxyphenyl)-N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 316832-49-2 HCAPLUS
CN L-Cysteine, S-(2,4-dimethylphenyl)-N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]- (9CI) (CA INDEX NAME)

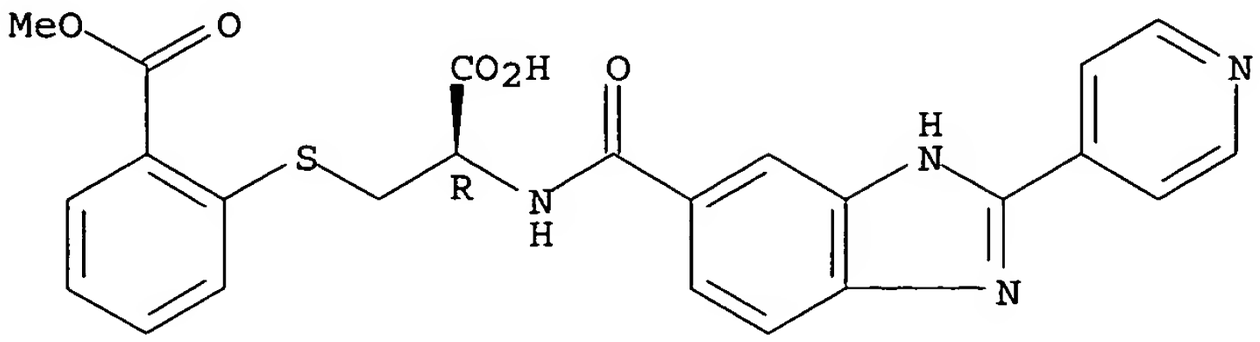
Absolute stereochemistry.



RN 316832-50-5 HCAPLUS
CN Benzoic acid, 2-[[(2R)-2-carboxy-2-[[[2-(4-pyridinyl)-1H-benzimidazol-5-

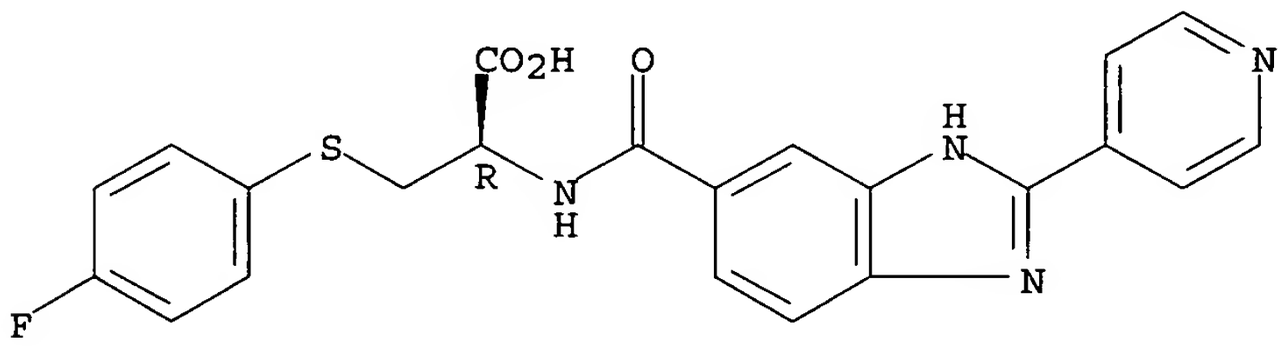
yl]carbonyl]amino]ethyl]thio]-, 1-methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



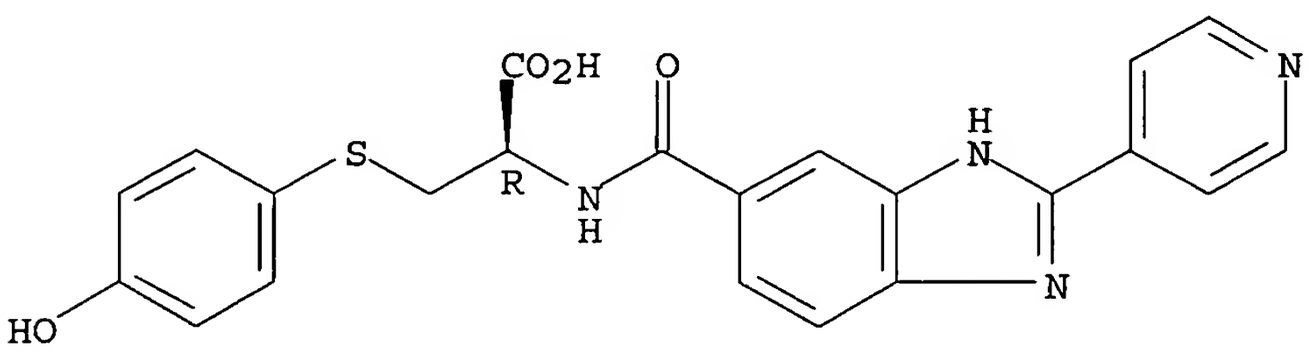
RN 316832-51-6 HCAPLUS
CN L-Cysteine, S-(4-fluorophenyl)-N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



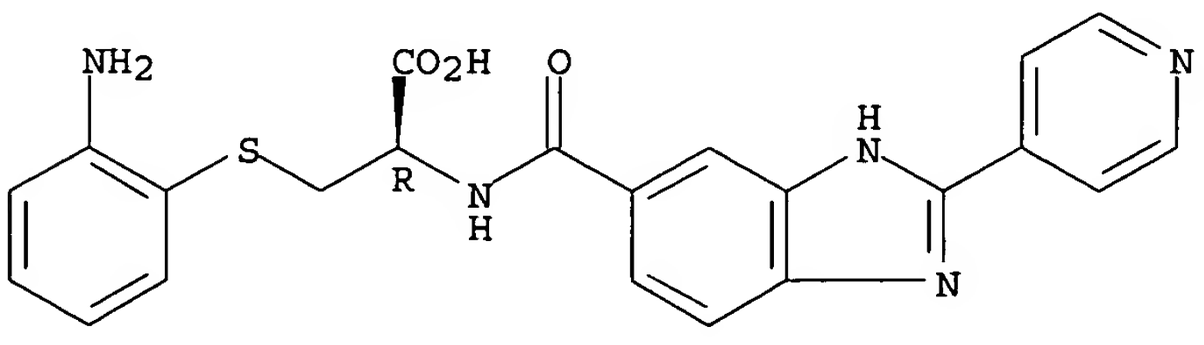
RN 316832-52-7 HCAPLUS
CN L-Cysteine, S-(4-hydroxyphenyl)-N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



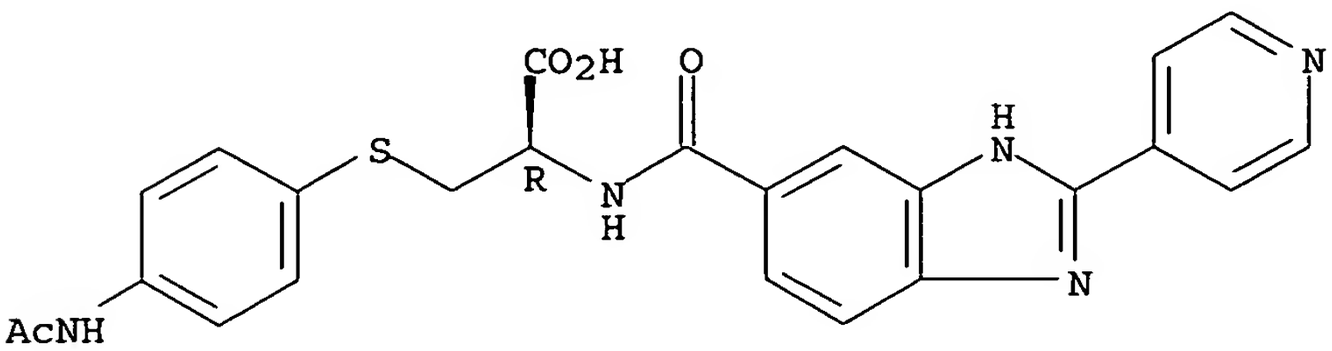
RN 316832-53-8 HCAPLUS
CN L-Cysteine, S-(2-aminophenyl)-N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



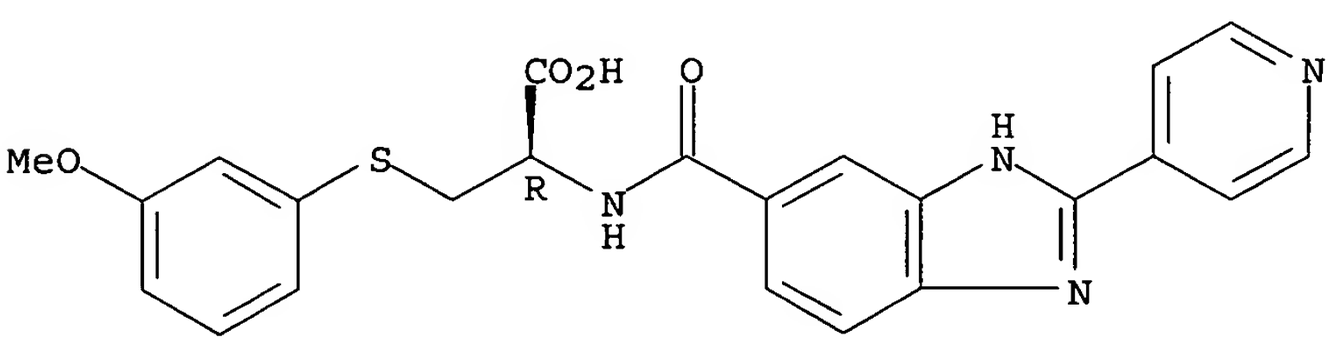
RN 316832-54-9 HCAPLUS
CN L-Cysteine, S-[4-(acetylamino)phenyl]-N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



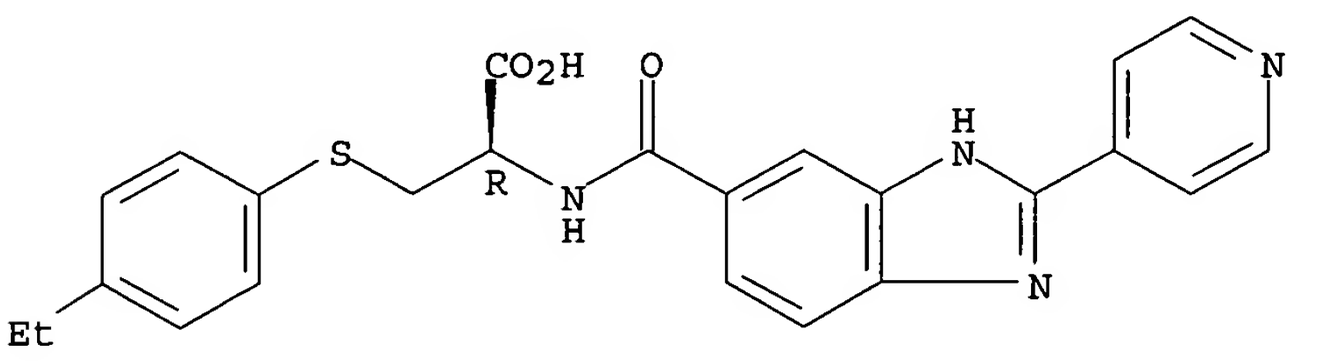
RN 316832-55-0 HCAPLUS
CN L-Cysteine, S-(3-methoxyphenyl)-N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



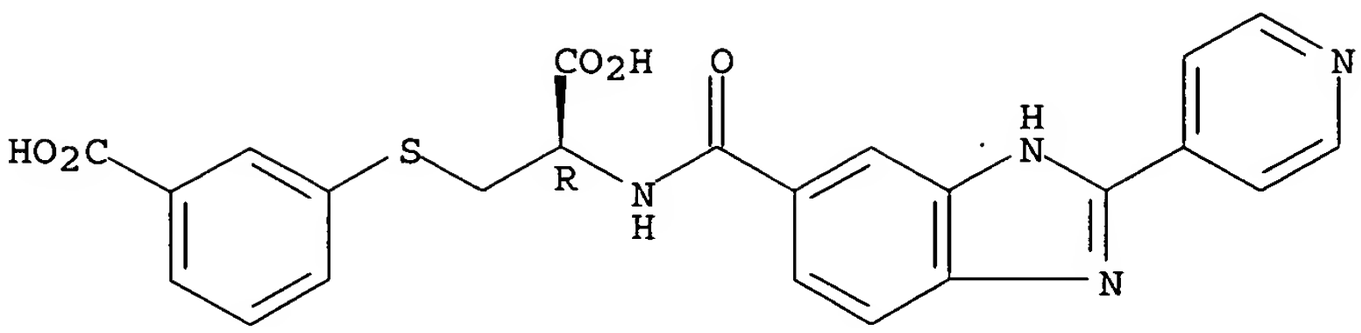
RN 316832-56-1 HCAPLUS
CN L-Cysteine, S-(4-ethylphenyl)-N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



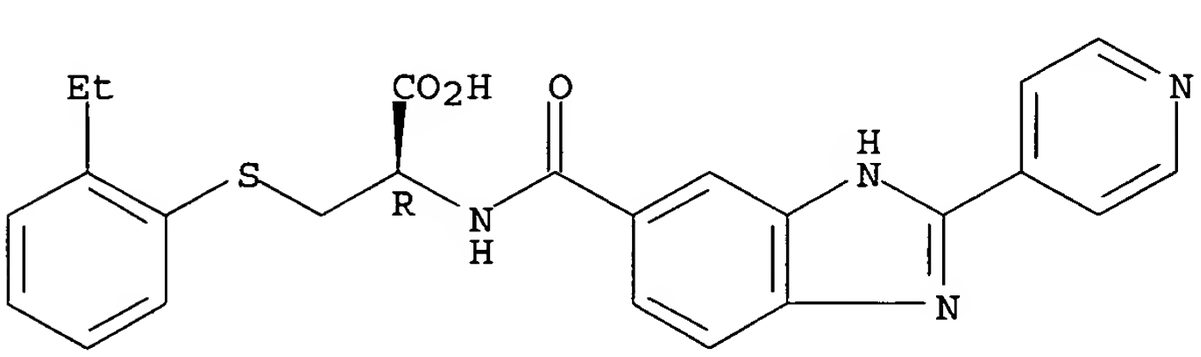
RN 316832-57-2 HCAPLUS
CN Benzoic acid, 3-[[(2R)-2-carboxy-2-[[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]amino]ethyl]thio]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



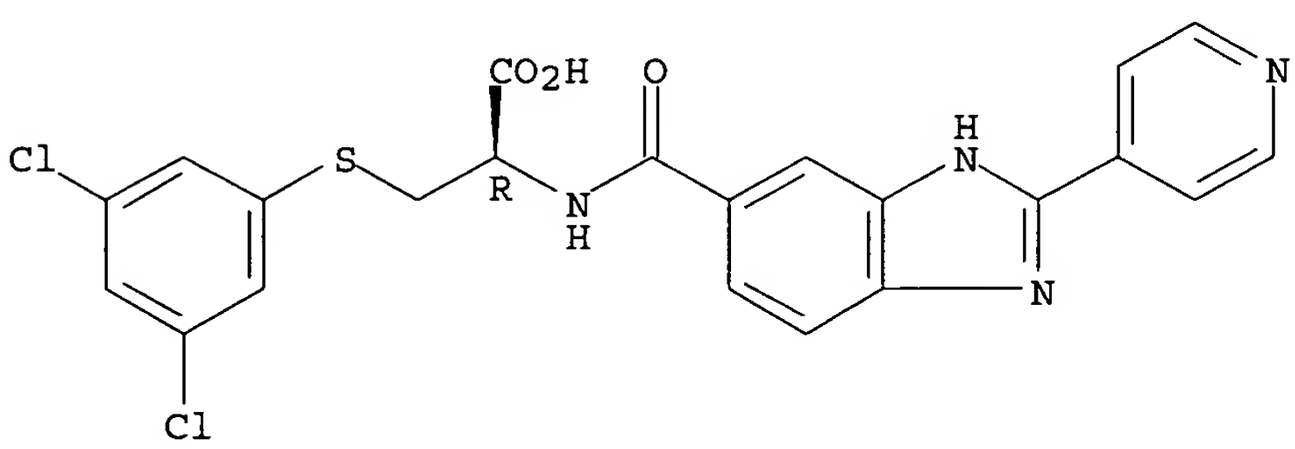
RN 316832-58-3 HCAPLUS
CN L-Cysteine, S-(2-ethylphenyl)-N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



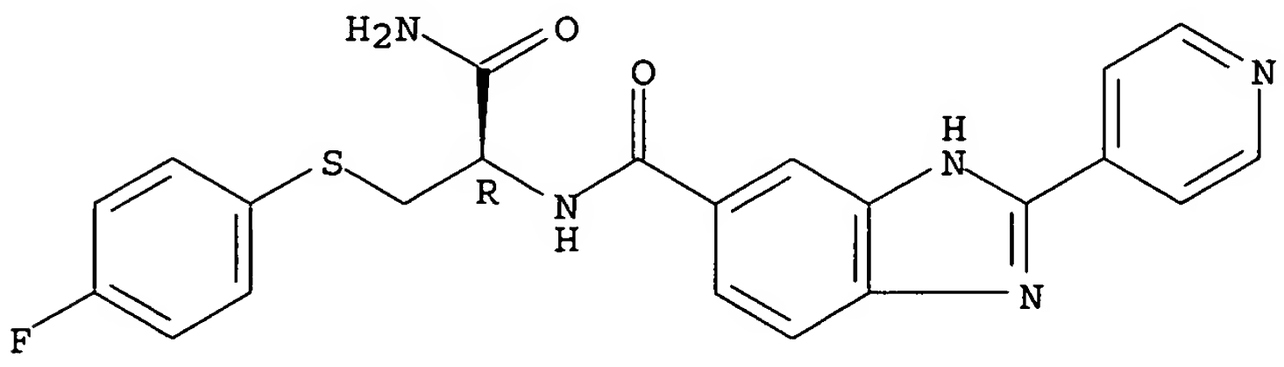
RN 316832-59-4 HCAPLUS
CN L-Cysteine, S-(3,5-dichlorophenyl)-N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



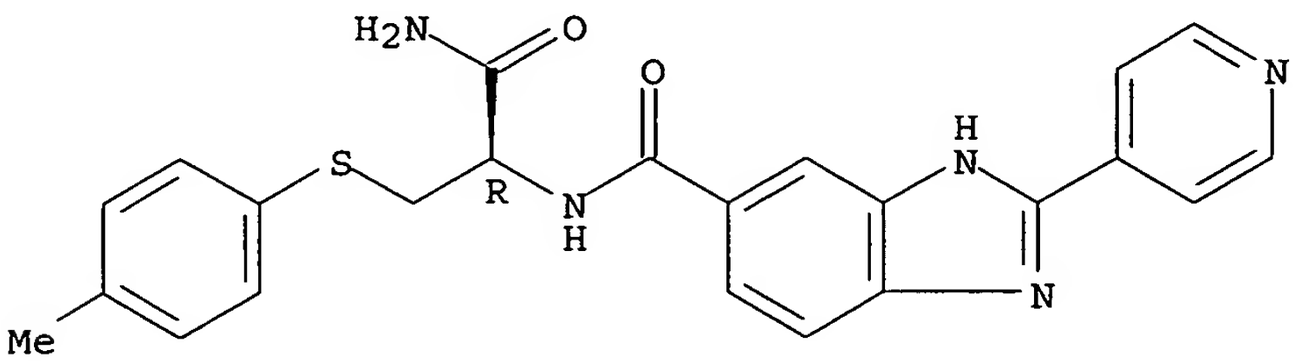
RN 316832-60-7 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1R)-2-amino-1-[[(4-fluorophenyl)thio]methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



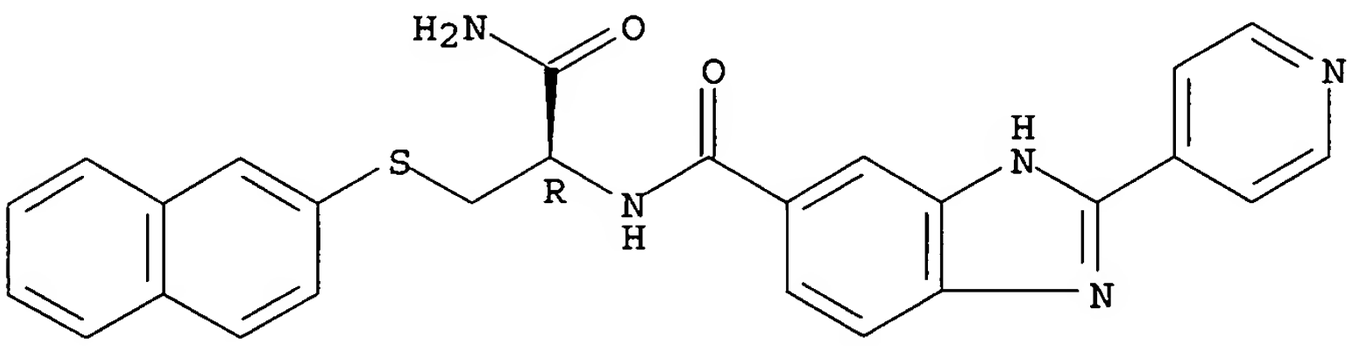
RN 316832-61-8 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1R)-2-amino-1-[[(4-methylphenyl)thio]methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



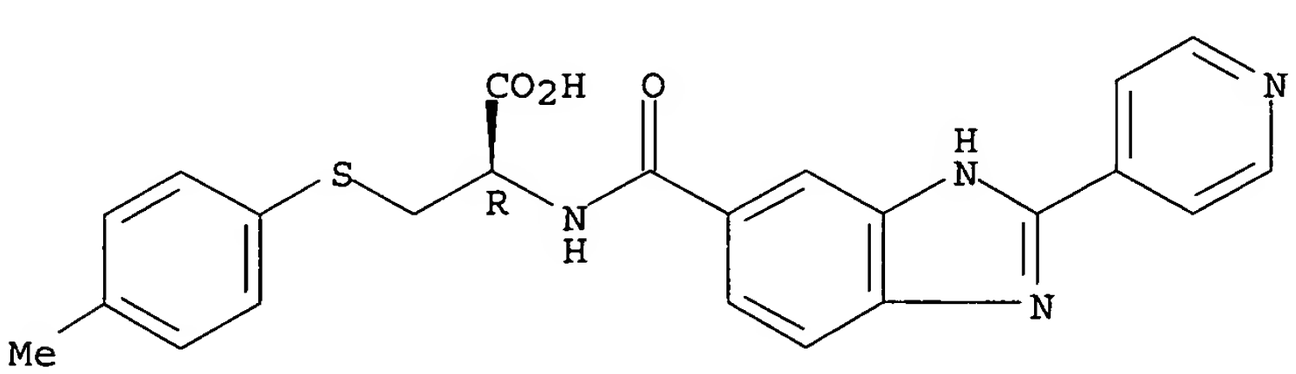
RN 316832-62-9 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1R)-2-amino-1-[(2-naphthalenylthio)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



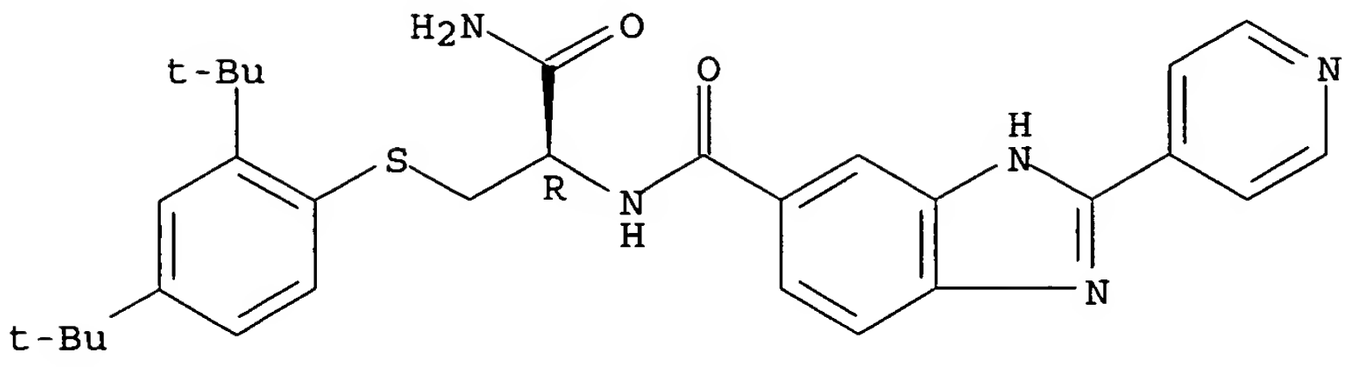
RN 316832-63-0 HCAPLUS
CN L-Cysteine, S-(4-methylphenyl)-N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



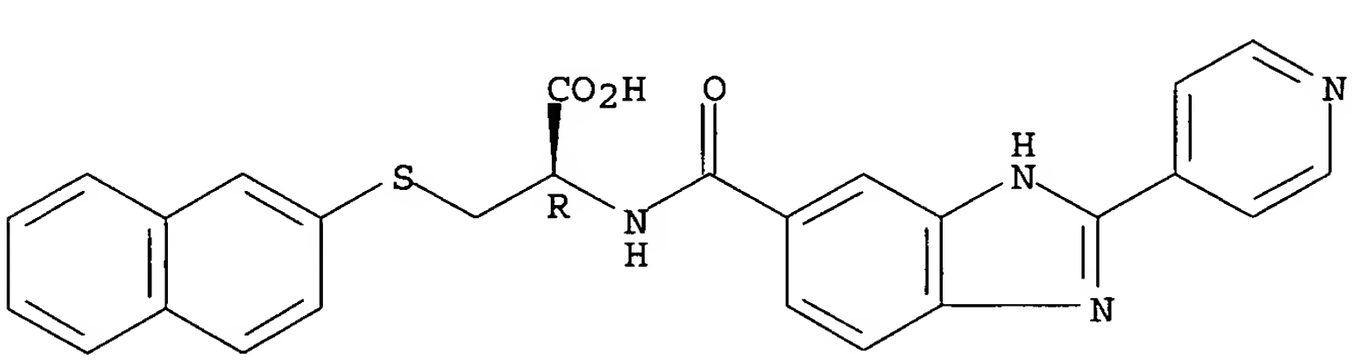
RN 316832-64-1 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1R)-2-amino-1-[[[2,4-bis(1,1-dimethylethyl)phenyl]thio]methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 316832-65-2 HCAPLUS
CN L-Cysteine, S-2-naphthalenyl-N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

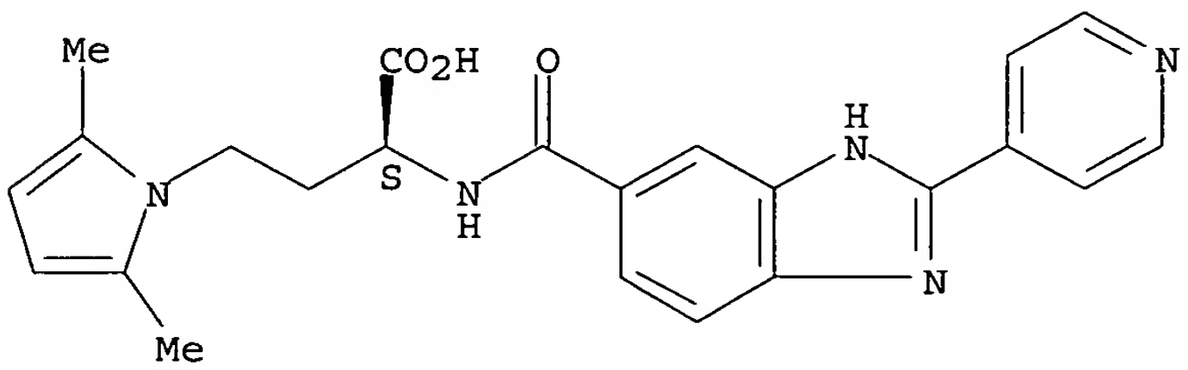


RN 316832-67-4 HCAPLUS
CN 1H-Pyrrole-1-butanoic acid, 2,5-dimethyl-α-[[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]amino]-, (αS)-, monoacetate (9CI) (CA INDEX NAME)

CM 1

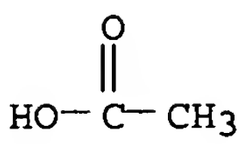
CRN 316832-66-3
CMF C23 H23 N5 O3

Absolute stereochemistry.



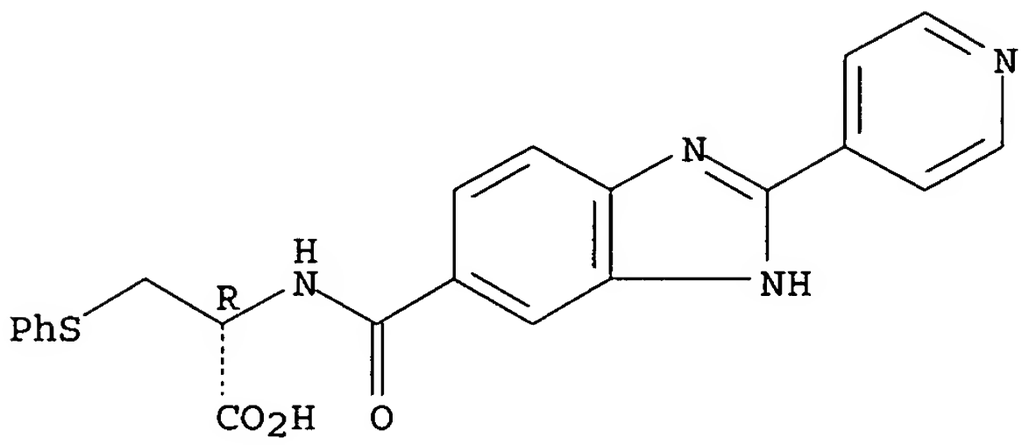
CM 2

CRN 64-19-7
CMF C2 H4 O2



RN 316832-68-5 HCAPLUS
CN L-Cysteine, S-phenyl-N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]-
(9CI) (CA INDEX NAME)

Absolute stereochemistry.

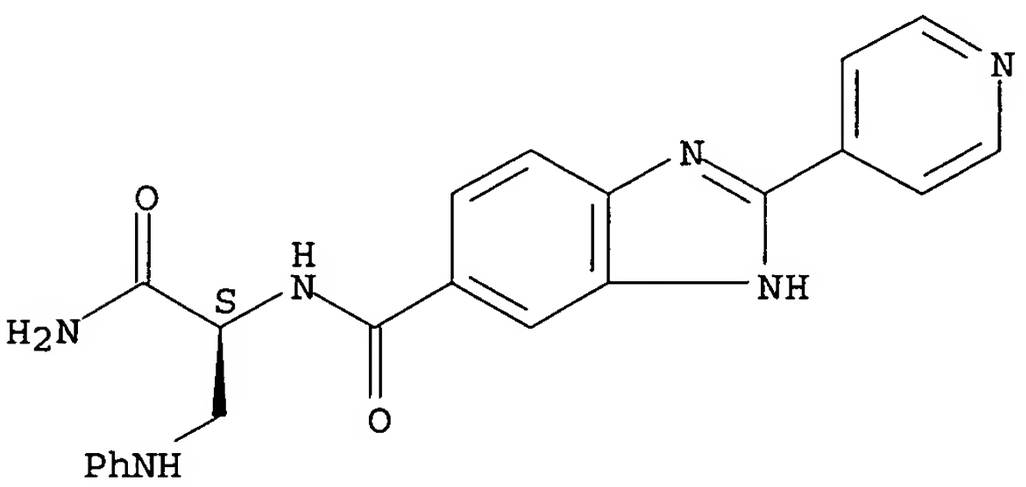


RN 316832-70-9 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-2-amino-2-oxo-1-
[(phenylamino)methyl]ethyl]-2-(4-pyridinyl)-, monoacetate (9CI) (CA INDEX
NAME)

CM 1

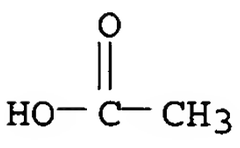
CRN 316832-69-6
CMF C22 H20 N6 O2

Absolute stereochemistry.



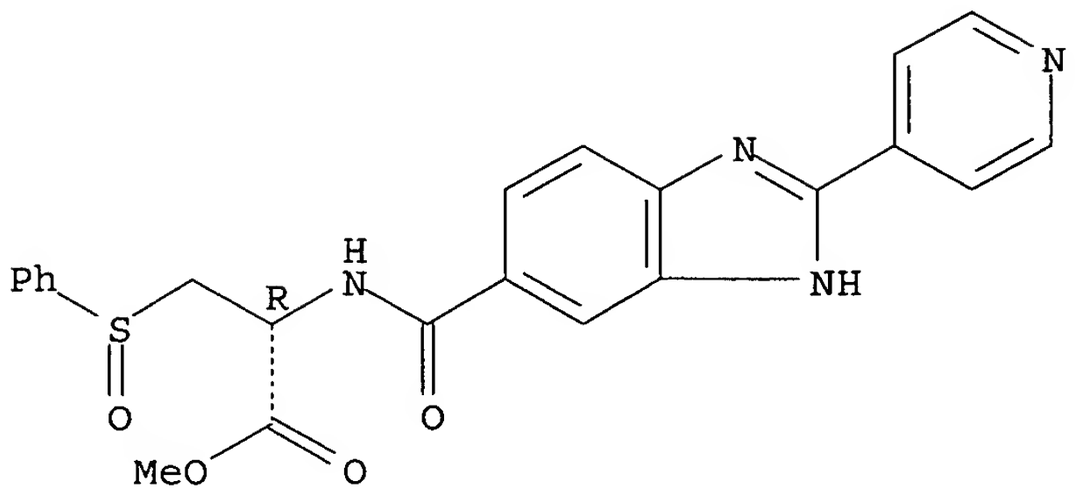
CM 2

CRN 64-19-7
CMF C2 H4 O2



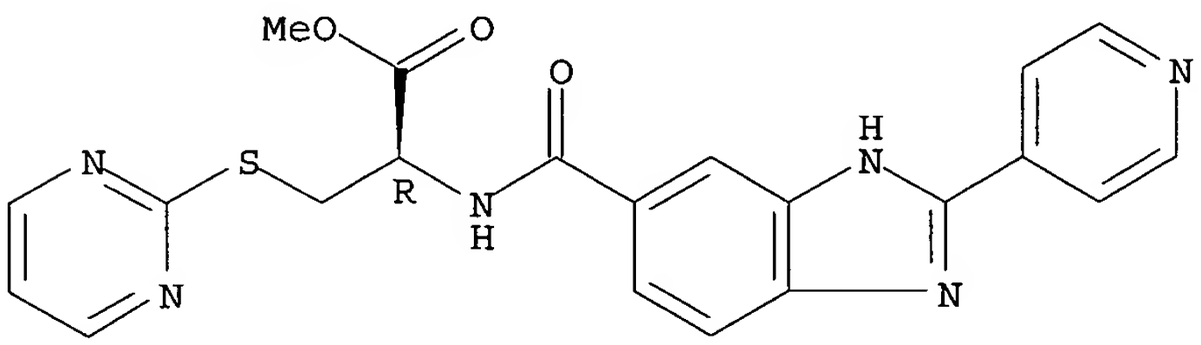
RN 316832-71-0 HCAPLUS
CN L-Alanine, 3-(phenylsulfinyl)-N-[[2-(4-pyridinyl)-1H-benzimidazol-5-
yl]carbonyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 316832-72-1 HCAPLUS
CN L-Cysteine, N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]-S-2-pyrimidinyl-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

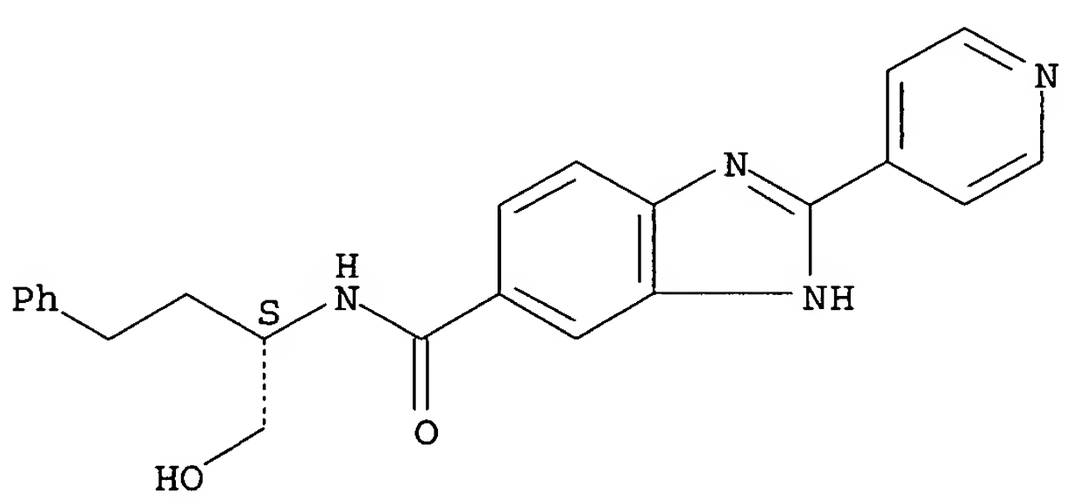


RN 316832-74-3 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-1-(hydroxymethyl)-3-phenylpropyl]-2-(4-pyridinyl)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

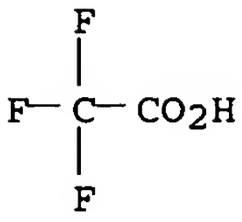
CRN 316832-73-2
CMF C23 H22 N4 O2

Absolute stereochemistry.



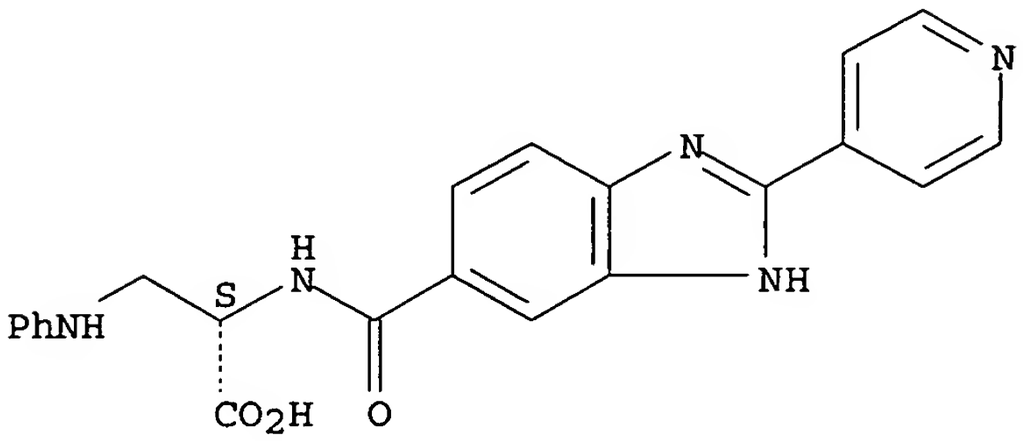
CM 2

CRN 76-05-1
CMF C2 H F3 O2



RN 316832-75-4 HCAPLUS
CN L-Alanine, 3-(phenylamino)-N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

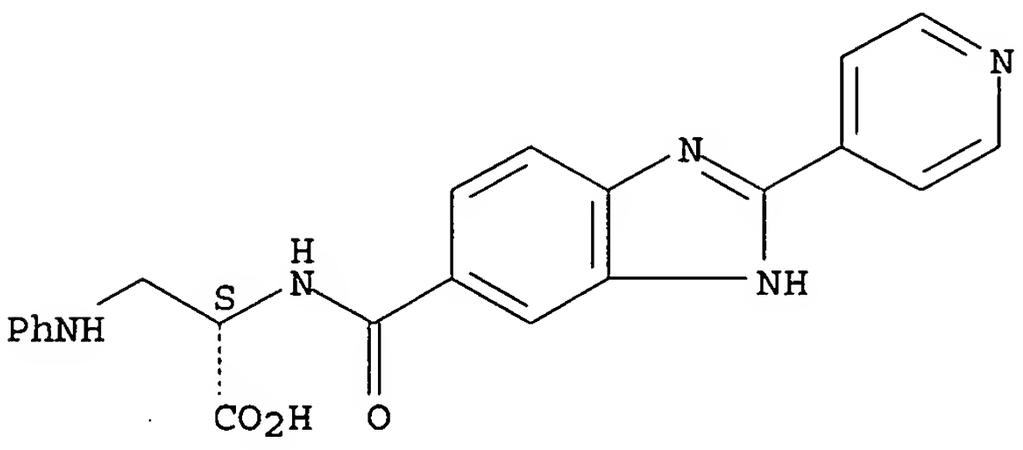


RN 316832-76-5 HCAPLUS
CN L-Alanine, 3-(phenylamino)-N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]-, monoacetate (9CI) (CA INDEX NAME)

CM 1

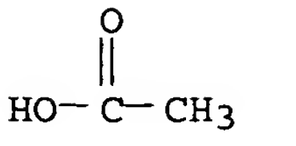
CRN 316832-75-4
CMF C22 H19 N5 O3

Absolute stereochemistry.



CM 2

CRN 64-19-7
CMF C2 H4 O2

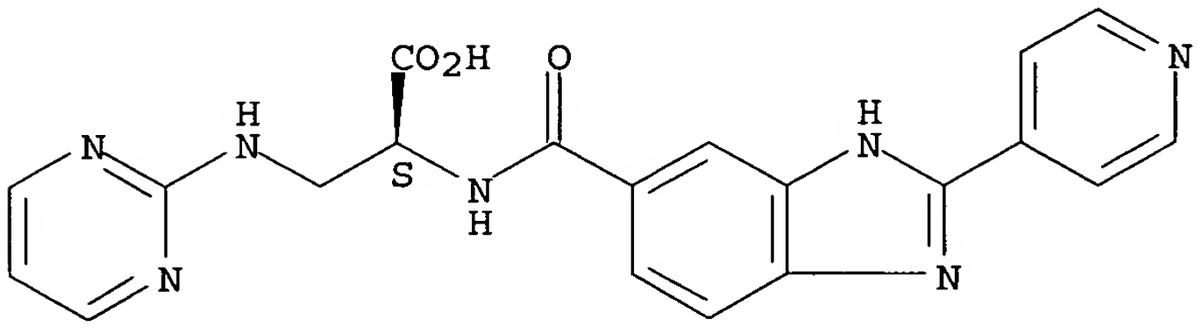


RN 316832-78-7 HCAPLUS
CN L-Alanine, N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]-3-(2-pyrimidinylamino)-, monoacetate (9CI) (CA INDEX NAME)

CM 1

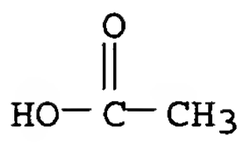
CRN 316832-77-6
CMF C20 H17 N7 O3

Absolute stereochemistry.



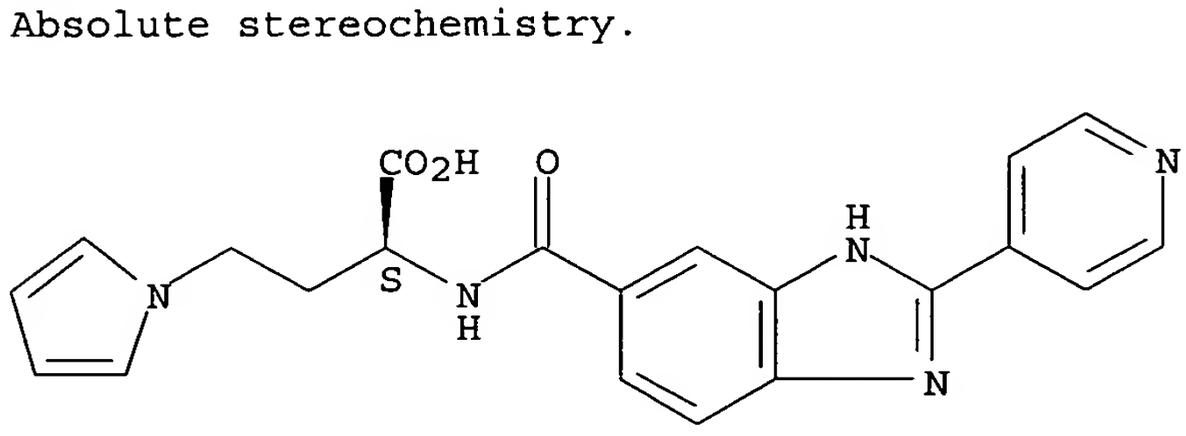
CM 2

CRN 64-19-7
CMF C2 H4 O2



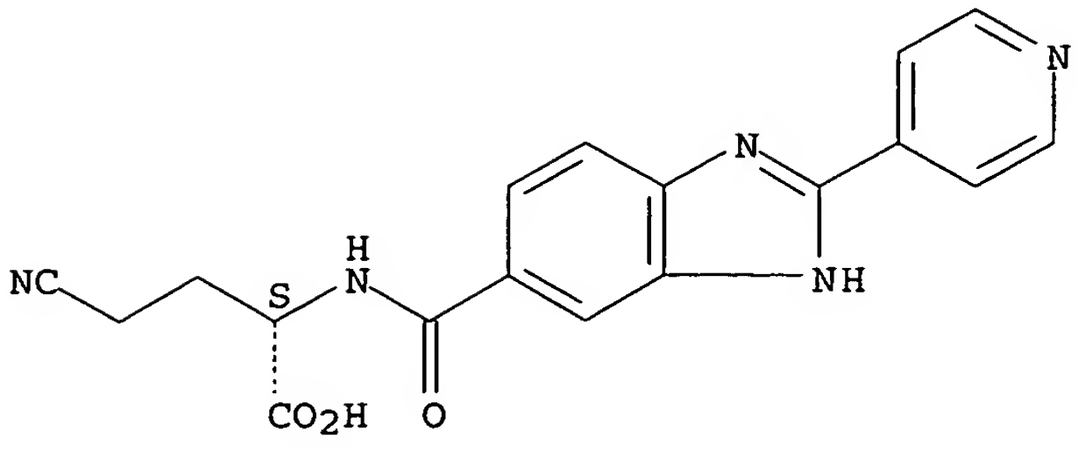
RN 316832-79-8 HCAPLUS
CN 1H-Pyrrole-1-butanoic acid, α-[[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]amino]-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 316832-80-1 HCAPLUS
CN Butanoic acid, 4-cyano-2-[[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]amino]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

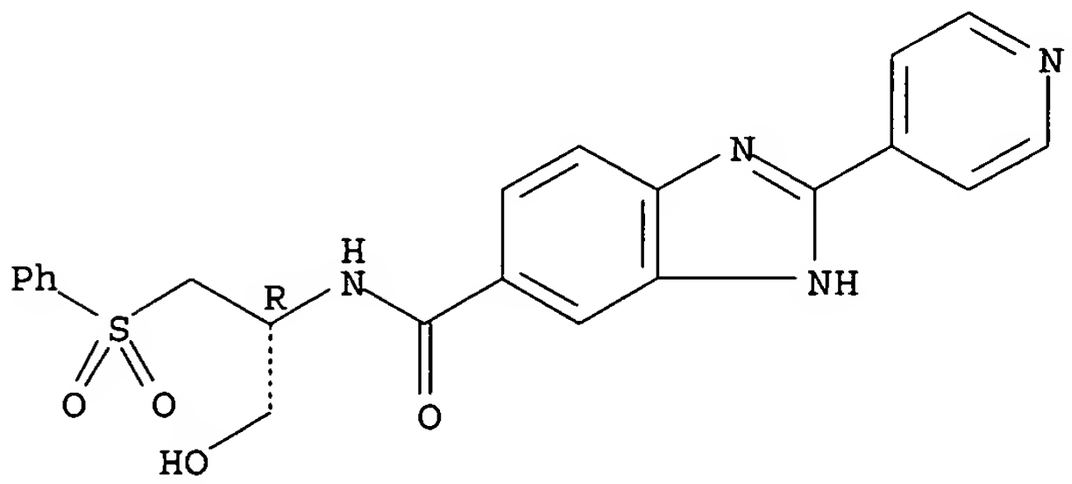


RN 316832-82-3 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1R)-1-(hydroxymethyl)-2-(phenylsulfonyl)ethyl]-2-(4-pyridinyl)-, monoacetate (salt) (9CI) (CA INDEX NAME)

CM 1

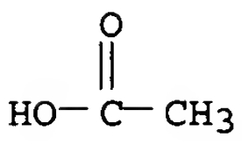
CRN 316832-81-2
CMF C22 H20 N4 O4 S

Absolute stereochemistry.



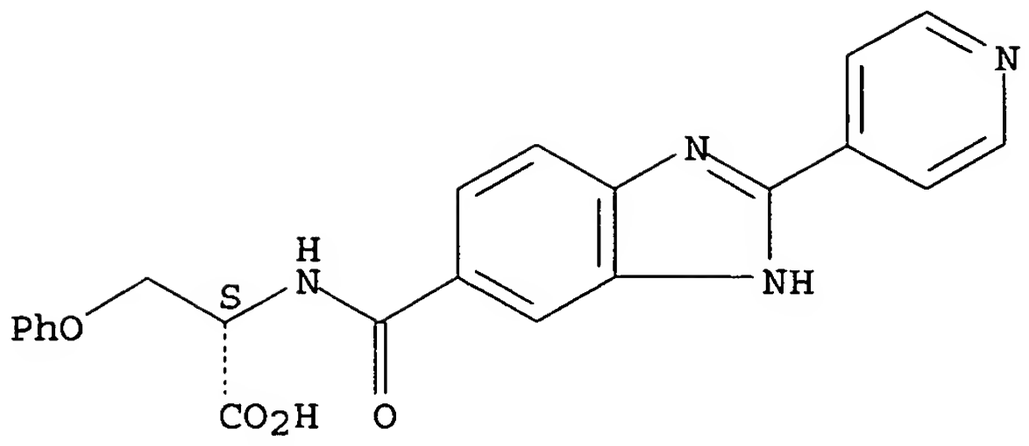
CM 2

CRN 64-19-7
CMF C2 H4 O2



RN 316832-83-4 HCAPLUS
CN L-Serine, O-phenyl-N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

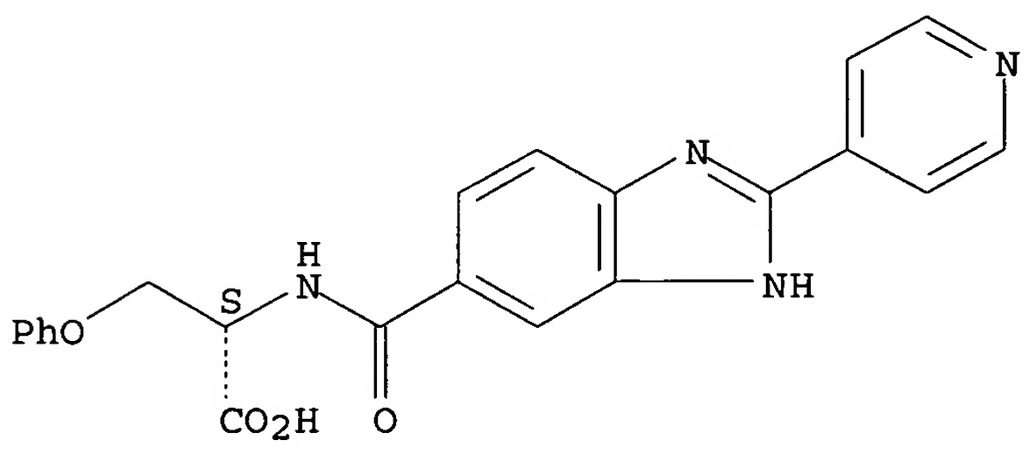


RN 316832-84-5 HCAPLUS
CN L-Serine, O-phenyl-N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]-, monoacetate (9CI) (CA INDEX NAME)

CM 1

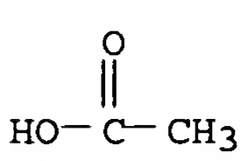
CRN 316832-83-4
CMF C22 H18 N4 O4

Absolute stereochemistry.



CM 2

CRN 64-19-7
CMF C2 H4 O2

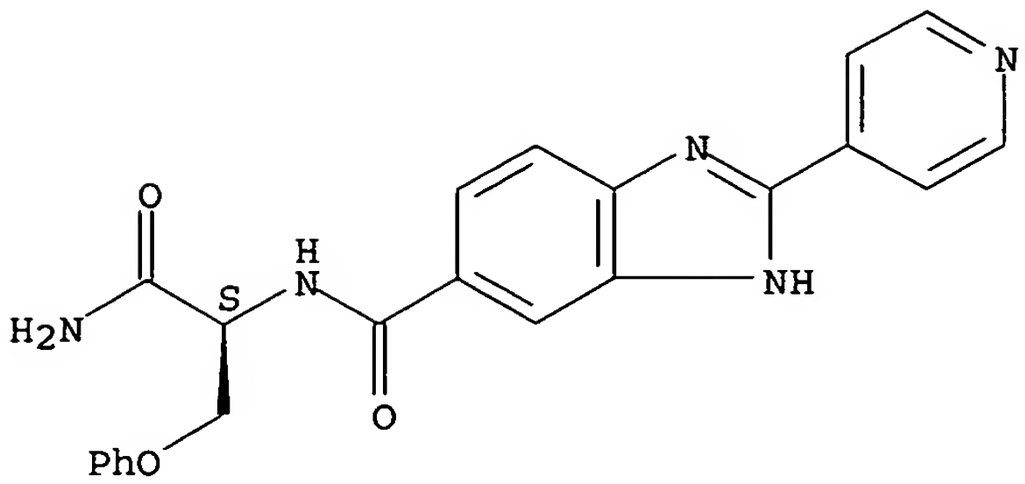


RN 316832-86-7 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-2-amino-2-oxo-1-(phenoxymethyl)ethyl]-2-(4-pyridinyl)-, monoacetate (9CI) (CA INDEX NAME)

CM 1

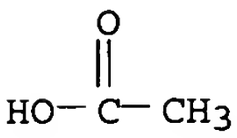
CRN 316832-85-6
CMF C22 H19 N5 O3

Absolute stereochemistry.



CM 2

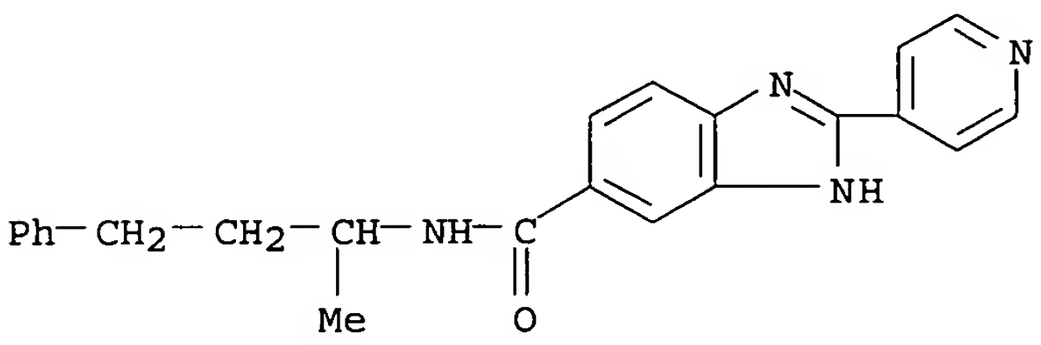
CRN 64-19-7
CMF C2 H4 O2



RN 316832-88-9 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-(1-methyl-3-phenylpropyl)-2-(4-pyridinyl)-, mono(trifluoroacetate) (9CI) (CA INDEX NAME)

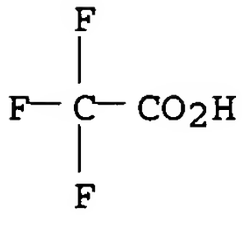
CM 1

CRN 316832-87-8
CMF C23 H22 N4 O



CM 2

CRN 76-05-1
CMF C2 H F3 O2

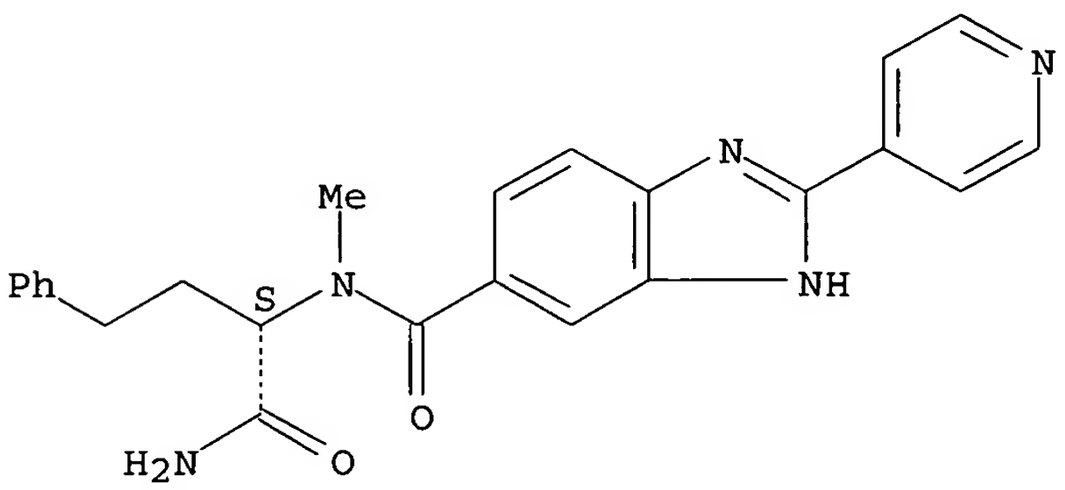


RN 316832-90-3 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-1-(aminocarbonyl)-3-phenylpropyl]-N-methyl-2-(4-pyridinyl)-, mono(trifluoroacetate) (9CI) (CA INDEX NAME)

CM 1

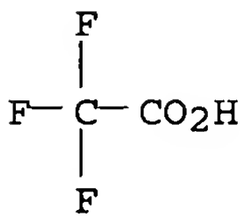
CRN 316832-89-0
CMF C24 H23 N5 O2

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

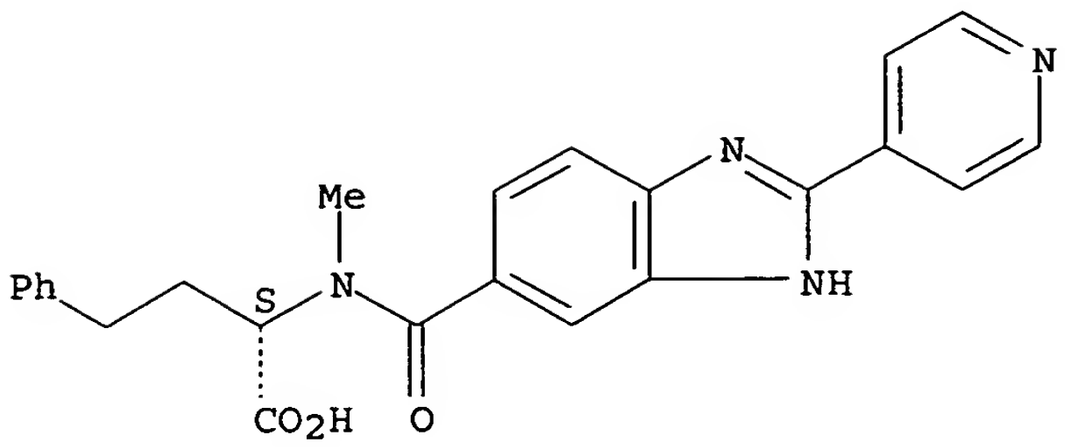


RN 316832-92-5 HCAPLUS
CN Benzenebutanoic acid, α-[methyl[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]amino]-, (αS)-, mono(trifluoroacetate) (9CI) (CA INDEX NAME)

CM 1

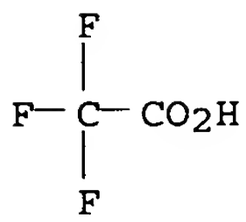
CRN 316832-91-4
CMF C24 H22 N4 O3

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

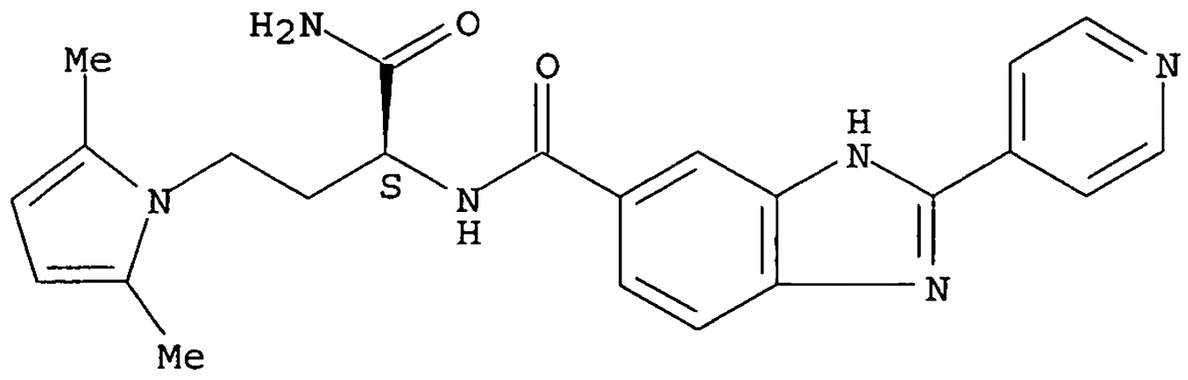


RN 316832-94-7 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-1-(aminocarbonyl)-3-(2,5-dimethyl-1H-pyrrol-1-yl)propyl]-2-(4-pyridinyl)-, monoacetate (9CI) (CA INDEX NAME)

CM 1

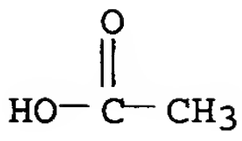
CRN 316832-93-6
CMF C23 H24 N6 O2

Absolute stereochemistry.



CM 2

CRN 64-19-7
CMF C2 H4 O2

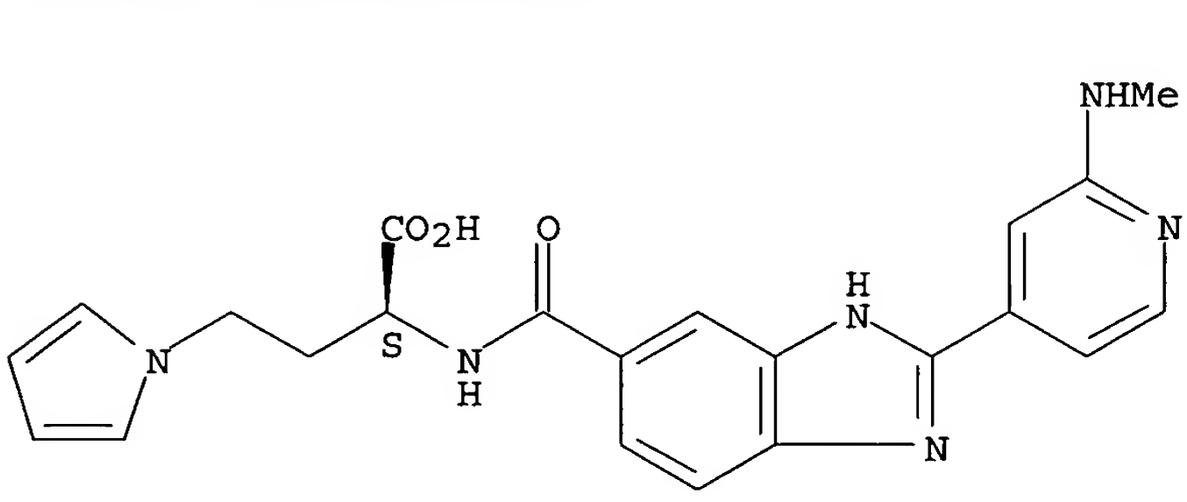


RN 316832-96-9 HCAPLUS
CN 1H-Pyrrole-1-butanoic acid, α-[[[2-[2-(methylamino)-4-pyridinyl]-1H-benzimidazol-5-yl]carbonyl]amino]-, (αS)-, mono(trifluoroacetate) (9CI) (CA INDEX NAME)

CM 1

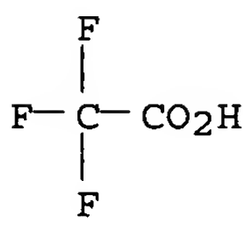
CRN 316832-95-8
CMF C22 H22 N6 O3

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

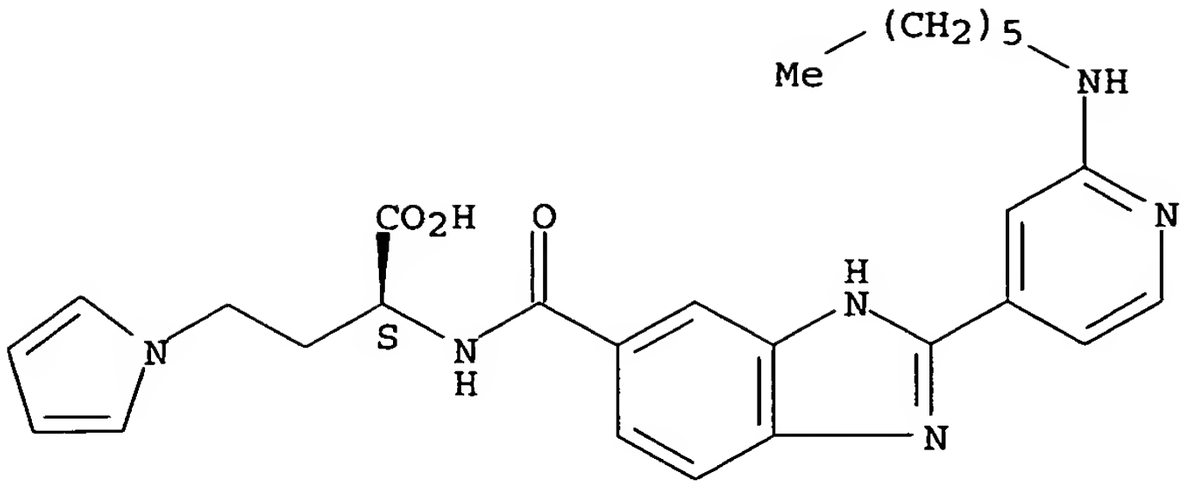


RN 316832-98-1 HCAPLUS
CN 1H-Pyrrole-1-butanoic acid, α-[[[2-[2-(hexylamino)-4-pyridinyl]-1H-benzimidazol-5-yl]carbonyl]amino]-, (αS)-, mono(trifluoroacetate) (9CI) (CA INDEX NAME)

CM 1

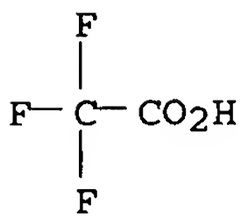
CRN 316832-97-0
CMF C27 H32 N6 O3

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

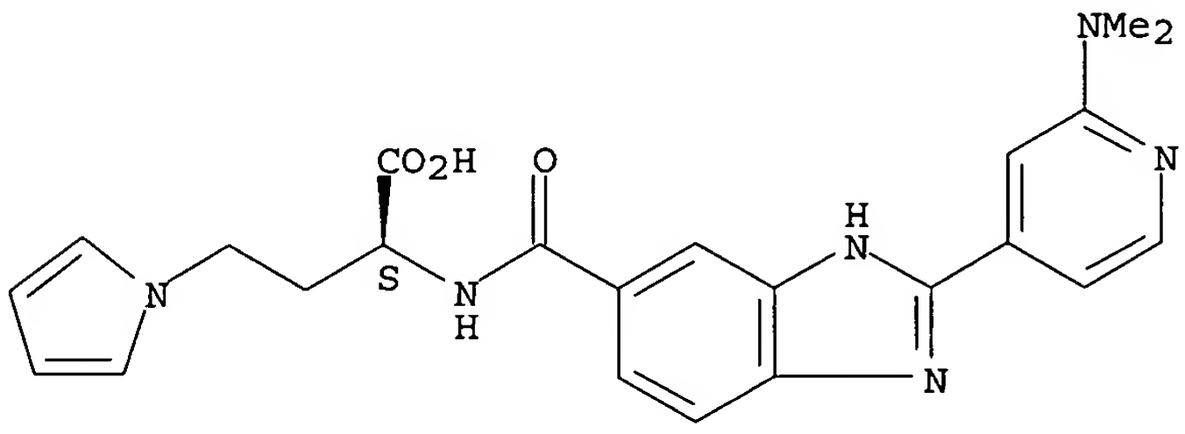


RN 316833-00-8 HCAPLUS
CN 1H-Pyrrole-1-butanoic acid, α-[[[2-[2-(dimethylamino)-4-pyridinyl]-1H-benzimidazol-5-yl]carbonyl]amino]-, (αS)-, mono(trifluoroacetate) (9CI) (CA INDEX NAME)

CM 1

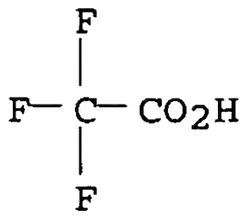
CRN 316832-99-2
CMF C23 H24 N6 O3

Absolute stereochemistry.



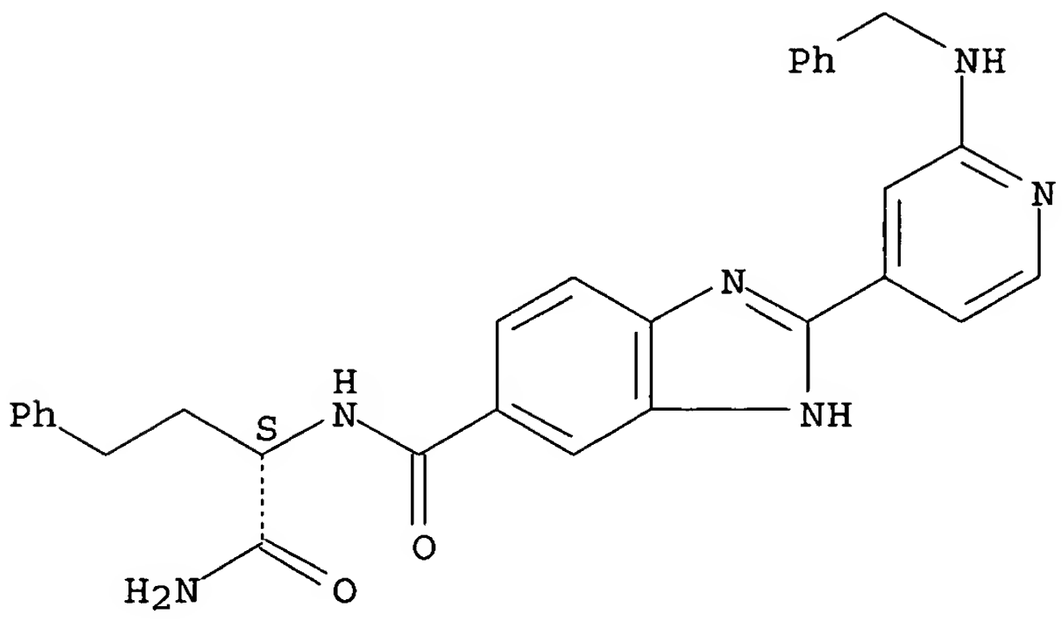
CM 2

CRN 76-05-1
CMF C2 H F3 O2



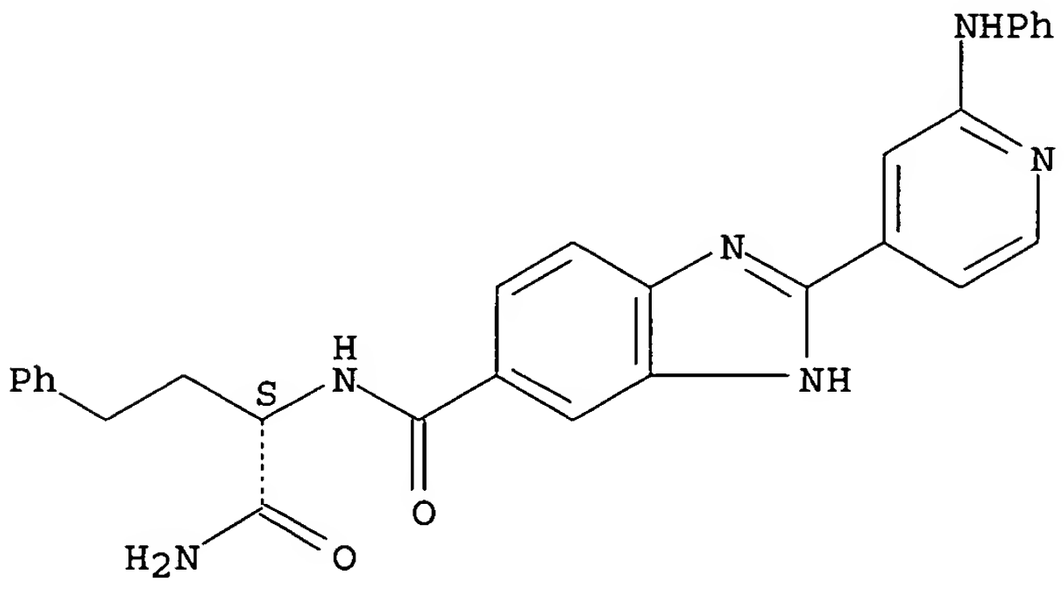
RN 316833-01-9 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-1-(aminocarbonyl)-3-phenylpropyl]-2-[2-[(phenylmethyl)amino]-4-pyridinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



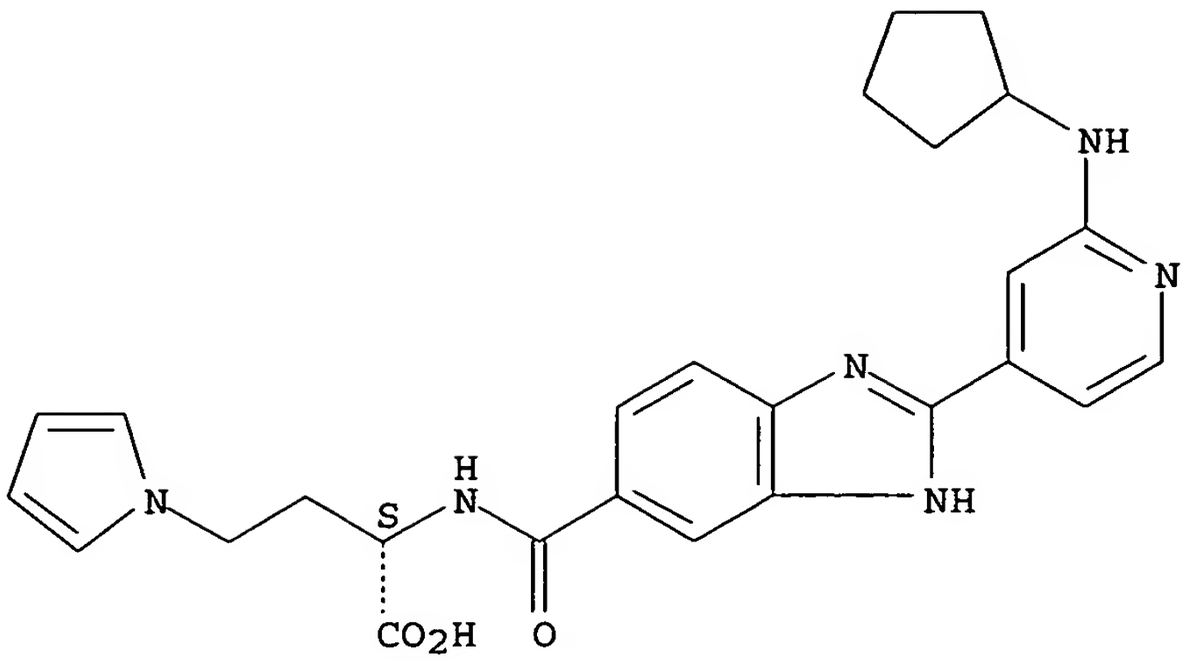
RN 316833-02-0 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-1-(aminocarbonyl)-3-phenylpropyl]-2-[2-(phenylamino)-4-pyridinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



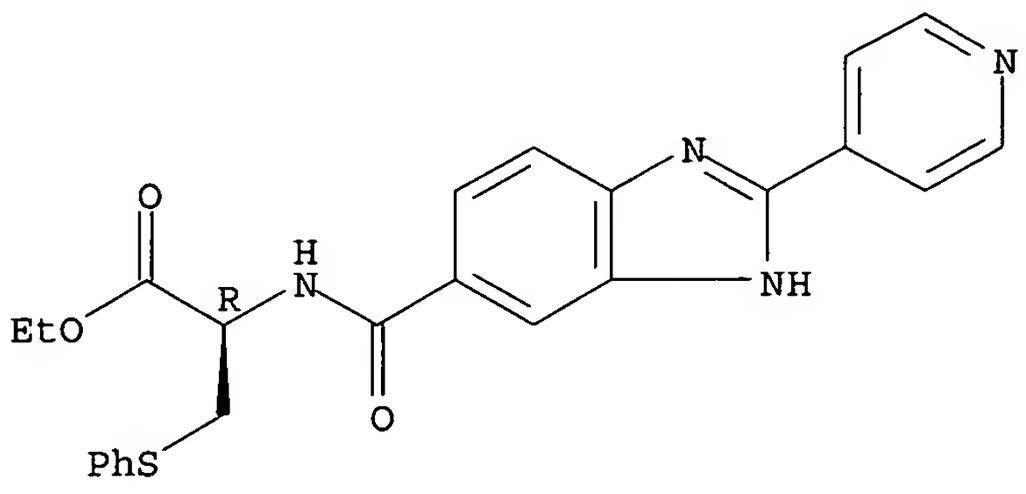
RN 316833-03-1 HCAPLUS
CN 1H-Pyrrole-1-butanoic acid, α-[[[2-[2-(cyclopentylamino)-4-pyridinyl]-1H-benzimidazol-5-yl]carbonyl]amino]-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



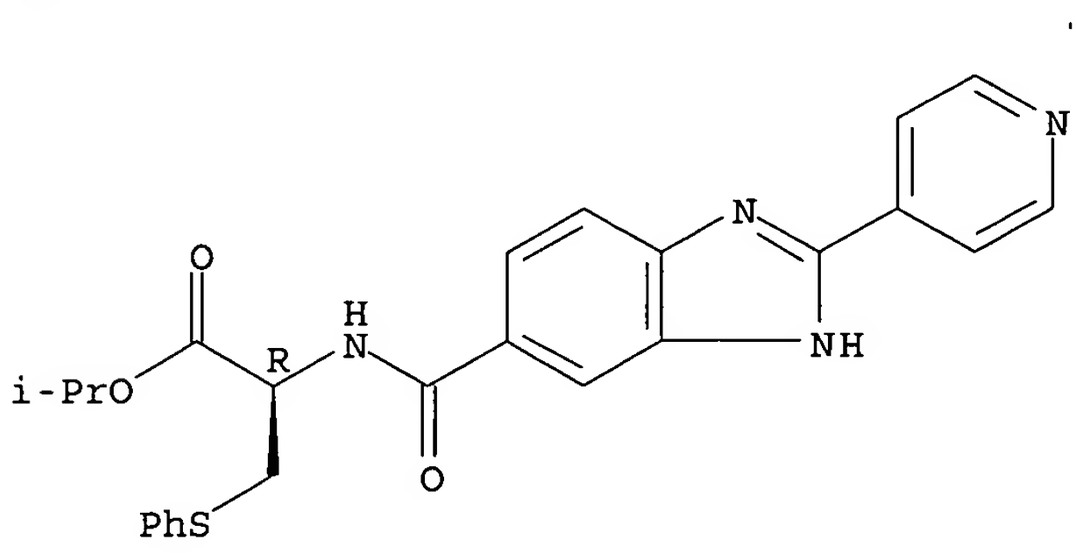
RN 316833-04-2 HCAPLUS
CN L-Cysteine, S-phenyl-N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



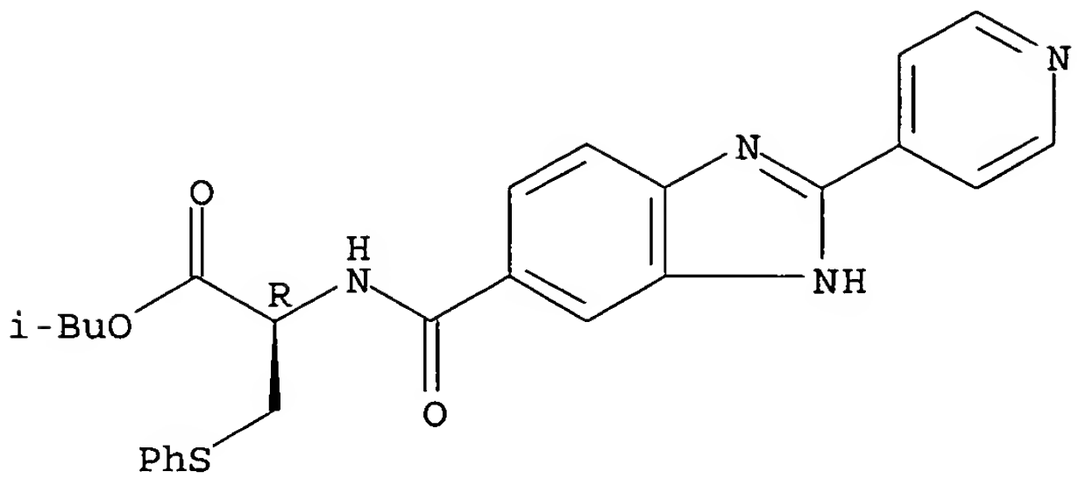
RN 316833-05-3 HCAPLUS
CN L-Cysteine, S-phenyl-N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]-, 1-methylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



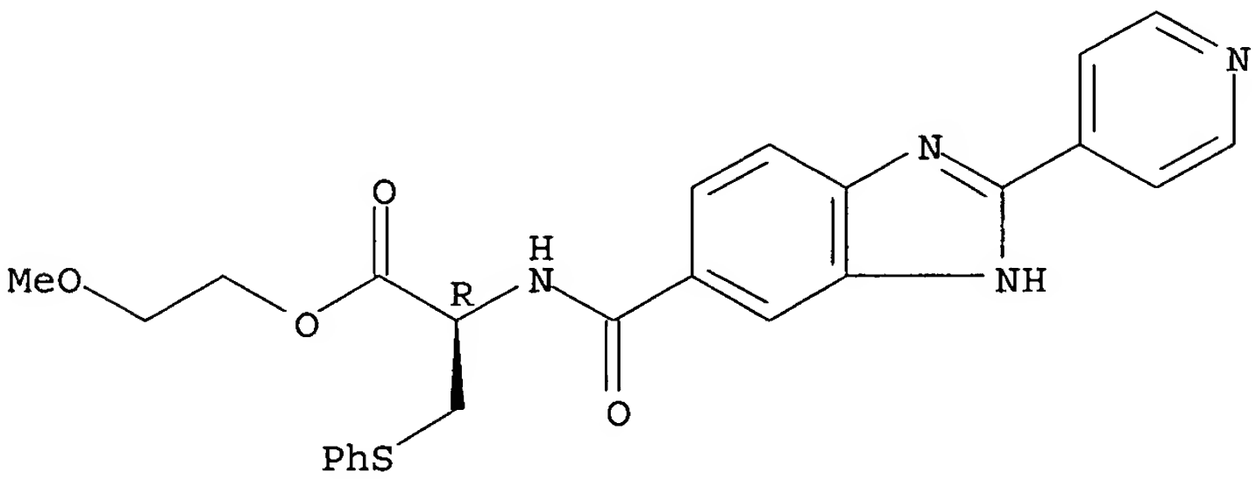
RN 316833-06-4 HCAPLUS
CN L-Cysteine, S-phenyl-N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]-, 2-methylpropyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



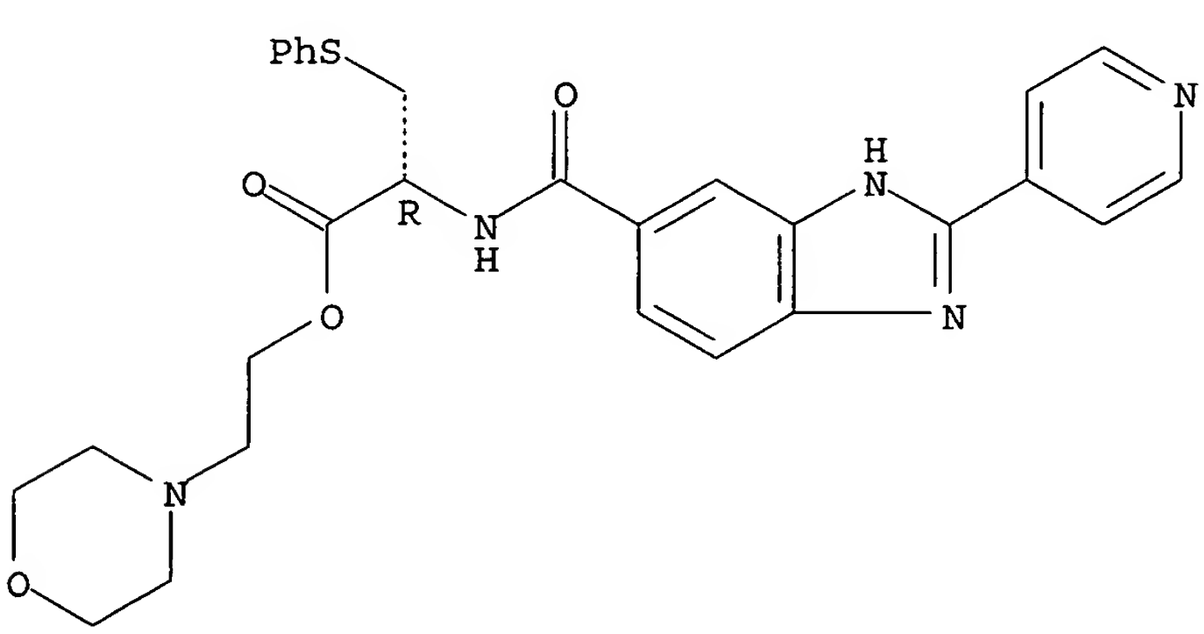
RN 316833-07-5 HCAPLUS
CN L-Cysteine, S-phenyl-N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]-, 2-methoxyethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



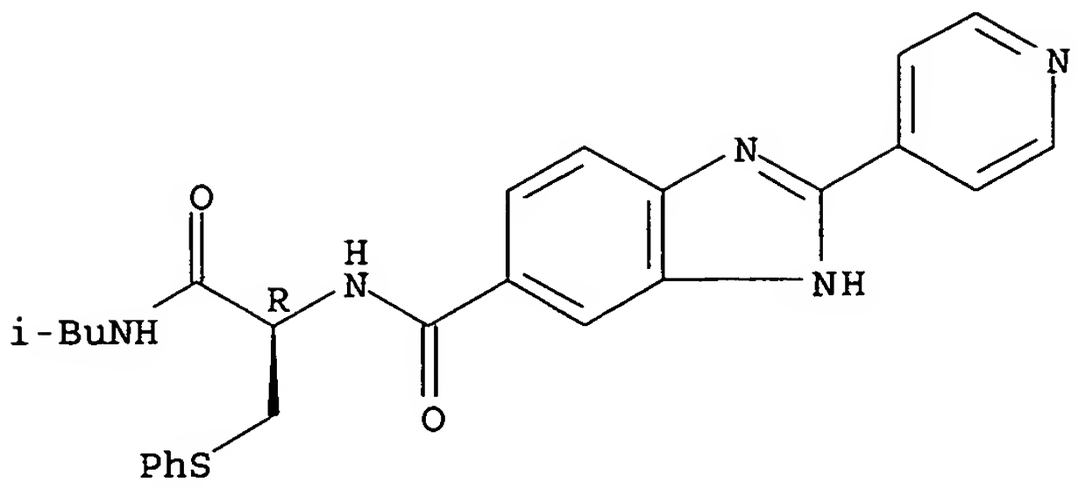
RN 316833-08-6 HCAPLUS
CN L-Cysteine, S-phenyl-N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]-, 2-(4-morpholinyl)ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



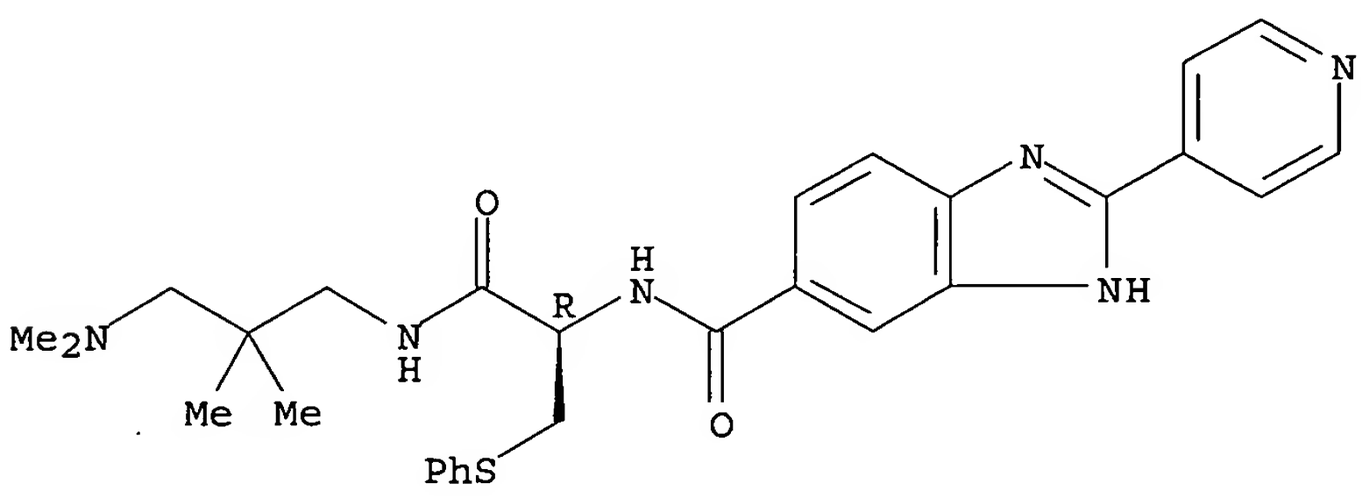
RN 316833-09-7 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1R)-2-[(2-methylpropyl)amino]-2-oxo-1-[(phenylthio)methyl]ethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



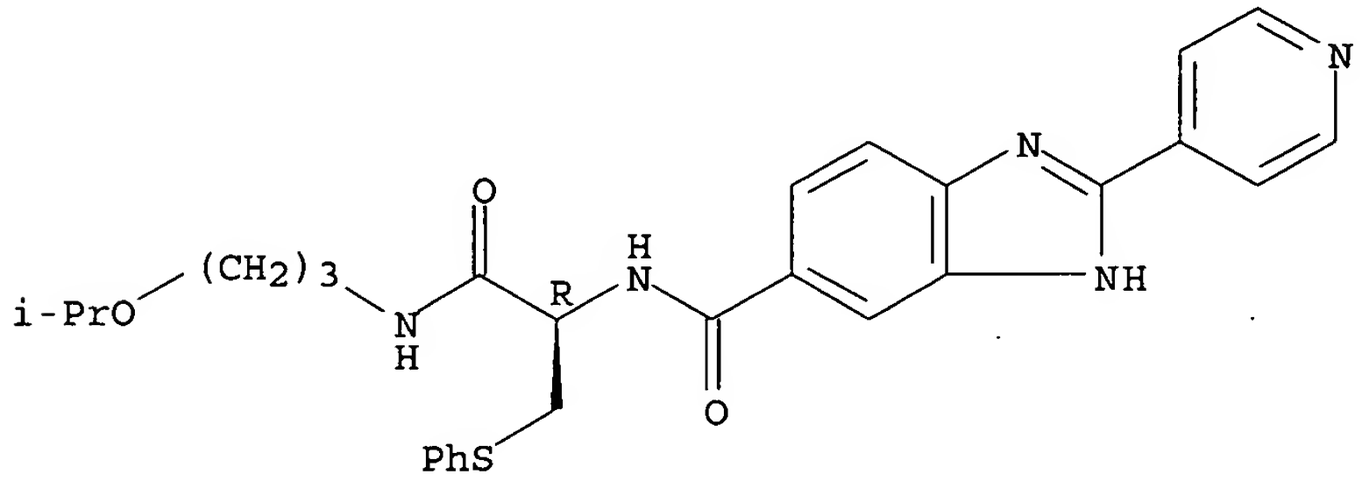
RN 316833-10-0 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1R)-2-[[3-(dimethylamino)-2,2-dimethylpropyl]amino]-2-oxo-1-[(phenylthio)methyl]ethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



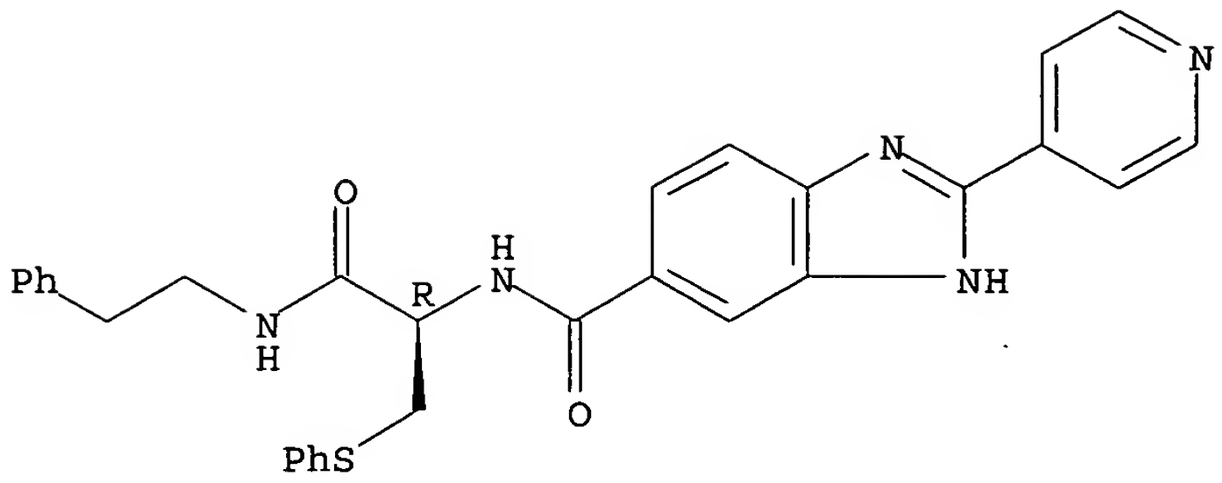
RN 316833-11-1 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1R)-2-[[3-(1-methylethoxy)propyl]amino]-2-oxo-1-[(phenylthio)methyl]ethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



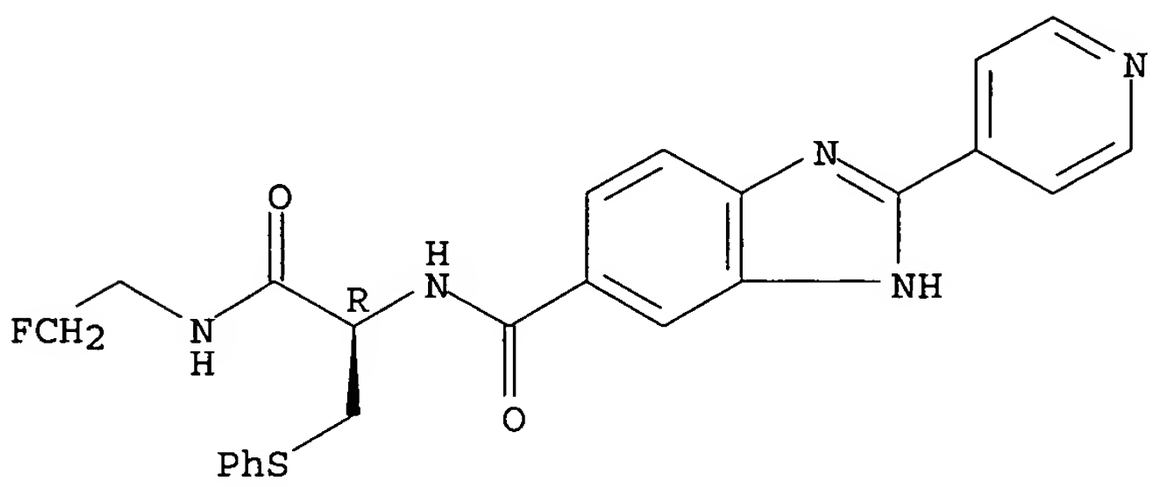
RN 316833-12-2 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1R)-2-oxo-2-[(2-phenylethyl)amino]-1-[(phenylthio)methyl]ethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



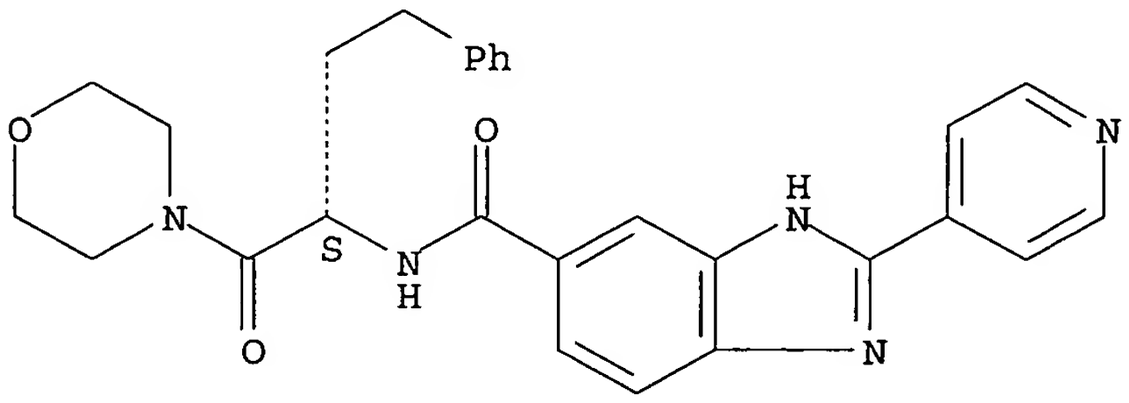
RN 316833-13-3 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1R)-2-[(2-fluoroethyl)amino]-2-oxo-1-[(phenylthio)methyl]ethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



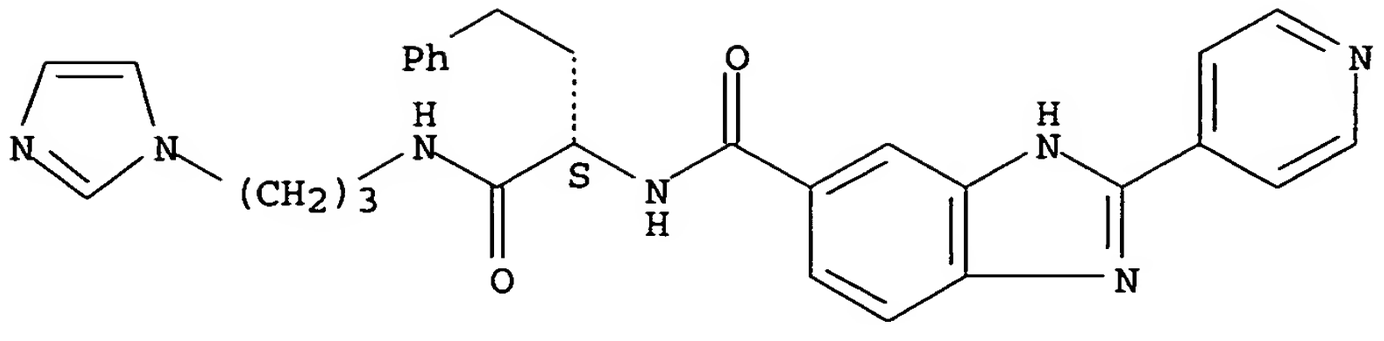
RN 316833-14-4 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-1-(4-morpholinylcarbonyl)-3-phenylpropyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



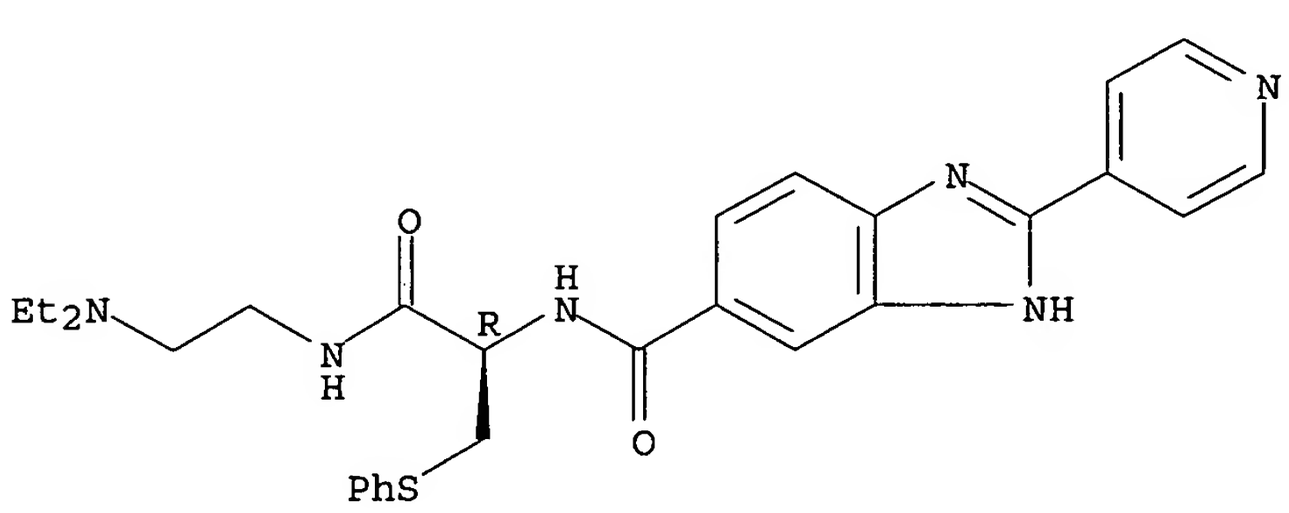
RN 316833-15-5 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-1-[[[3-(1H-imidazol-1-yl)propyl]amino]carbonyl]-3-phenylpropyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



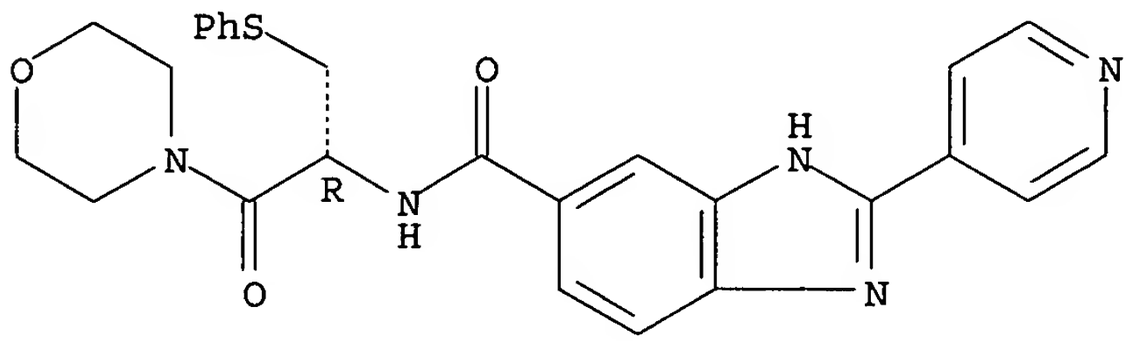
RN 316833-16-6 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1R)-2-[[2-(diethylamino)ethyl]amino]-2-oxo-1-[(phenylthio)methyl]ethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



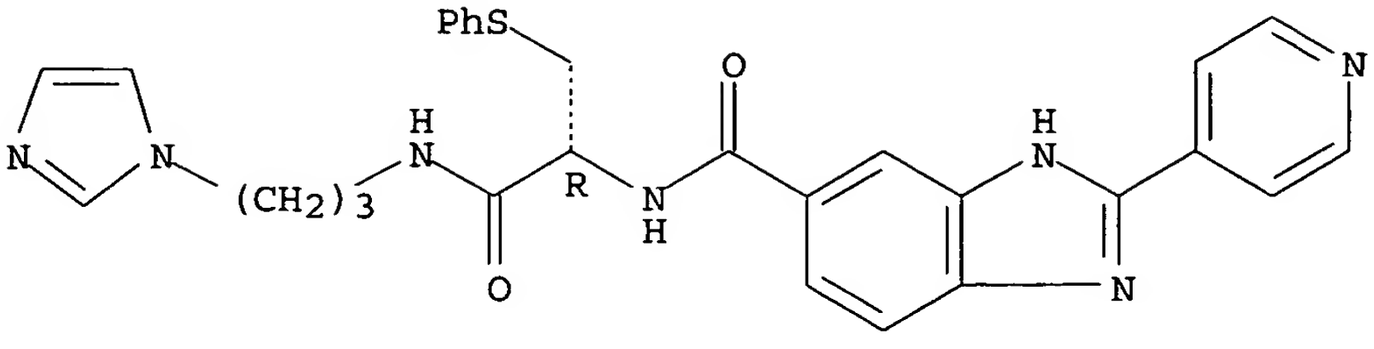
RN 316833-17-7 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1R)-2-(4-morpholinyl)-2-oxo-1-[(phenylthio)methyl]ethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



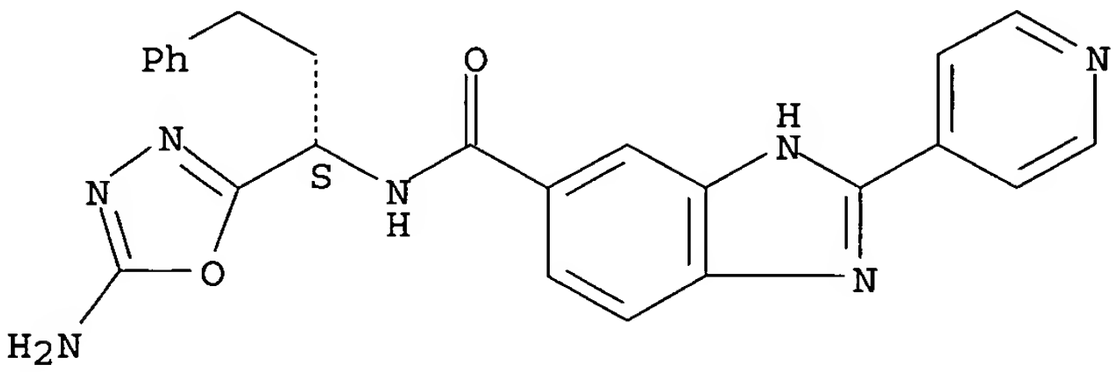
RN 316833-18-8 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1R)-2-[[3-(1H-imidazol-1-yl)propyl]amino]-2-oxo-1-[(phenylthio)methyl]ethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



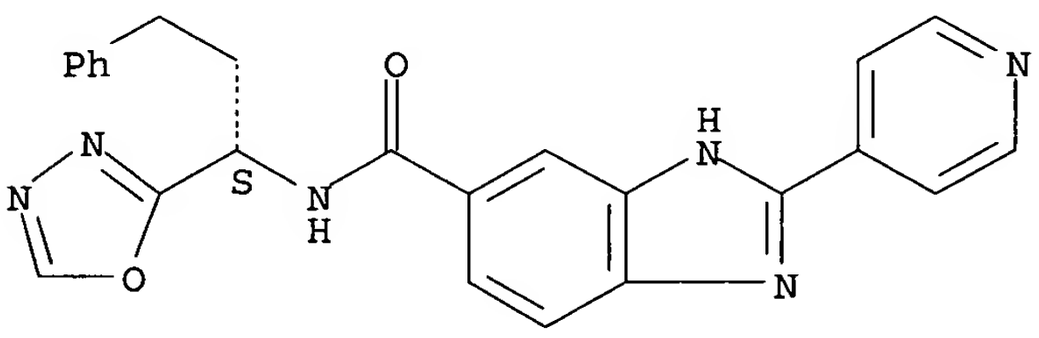
RN 316833-19-9 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-1-(5-amino-1,3,4-oxadiazol-2-yl)-3-phenylpropyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



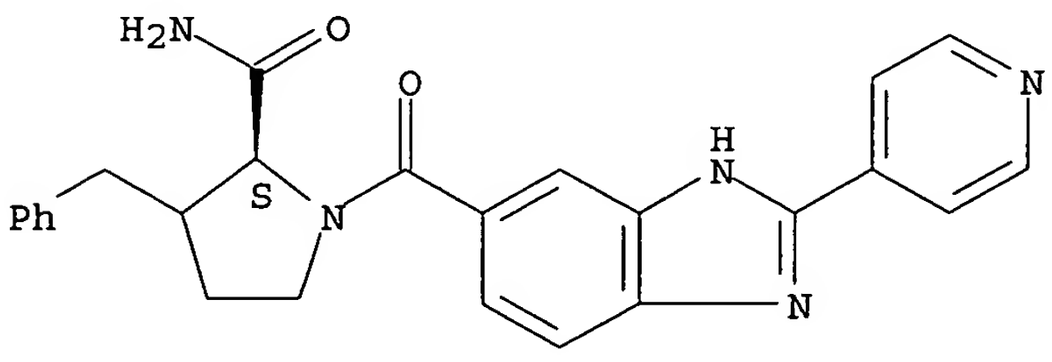
RN 316833-20-2 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-1-(1,3,4-oxadiazol-2-yl)-3-phenylpropyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 316833-21-3 HCAPLUS
CN 2-Pyrrolidinecarboxamide, 3-(phenylmethyl)-1-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]-, (2S)- (9CI) (CA INDEX NAME)

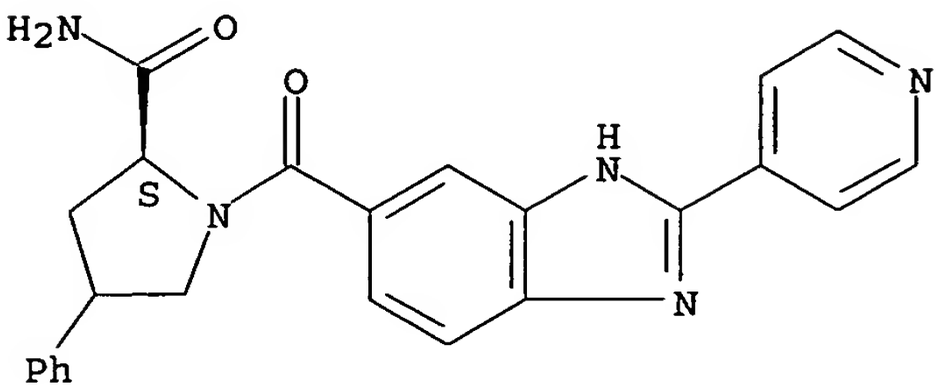
Absolute stereochemistry.



RN 316833-22-4 HCAPLUS
CN 2-Pyrrolidinecarboxamide, 4-phenyl-1-[[2-(4-pyridinyl)-1H-benzimidazol-5-

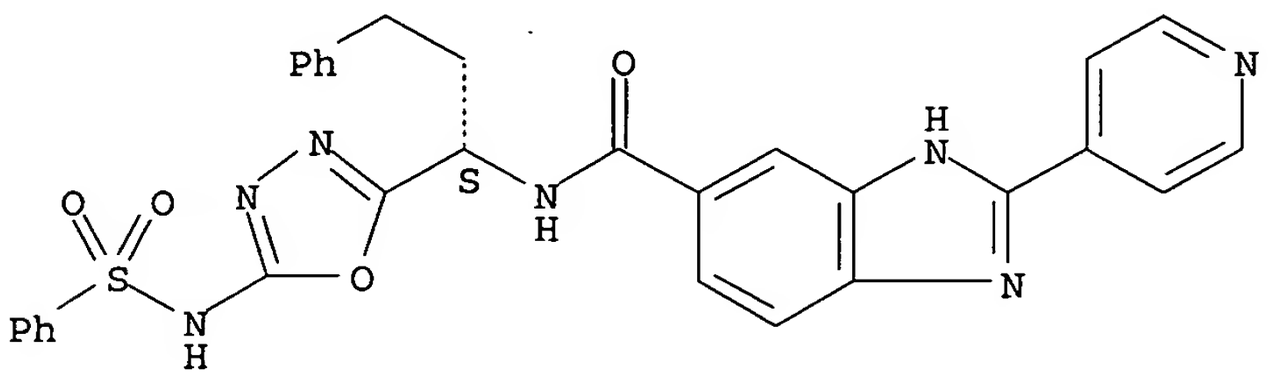
yl]carbonyl]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



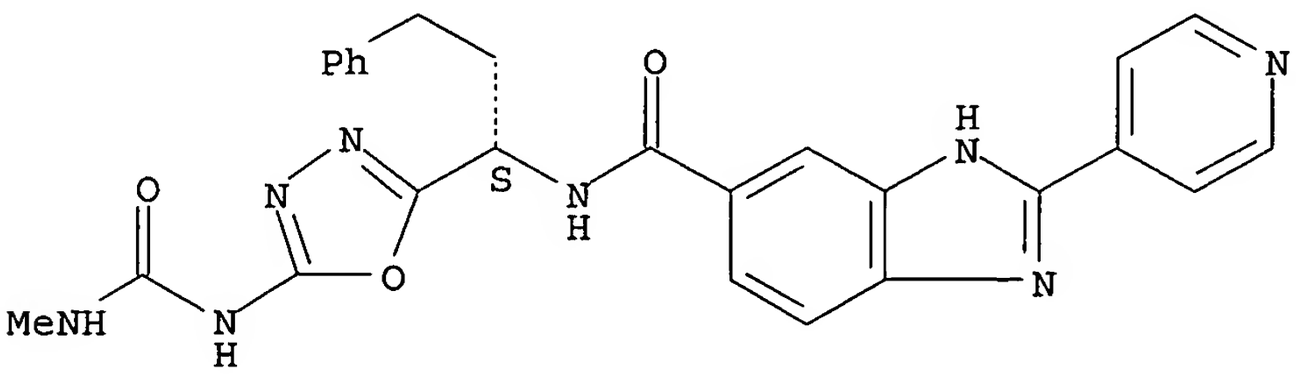
RN 316833-23-5 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-3-phenyl-1-[5-[(phenylsulfonyl)amino]-1,3,4-oxadiazol-2-yl]propyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



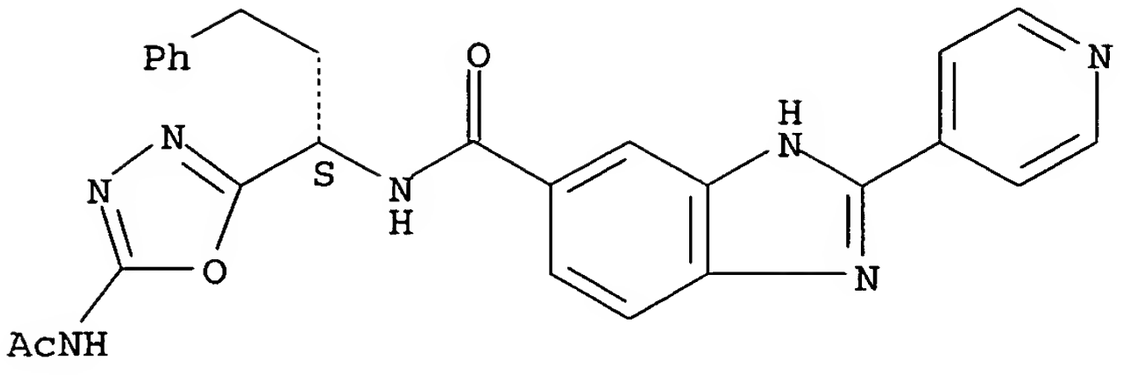
RN 316833-24-6 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-1-[5-[[(methylamino)carbonyl]amino]-1,3,4-oxadiazol-2-yl]-3-phenylpropyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



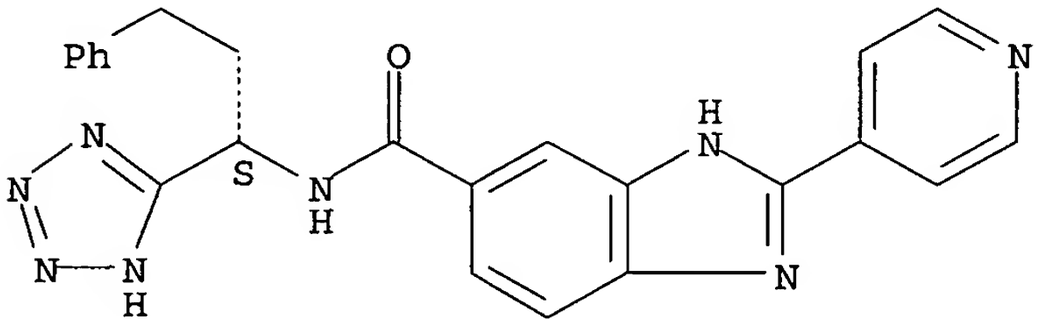
RN 316833-25-7 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-1-[5-(acetylamino)-1,3,4-oxadiazol-2-yl]-3-phenylpropyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 316833-26-8 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-3-phenyl-1-(1H-tetrazol-5-yl)propyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

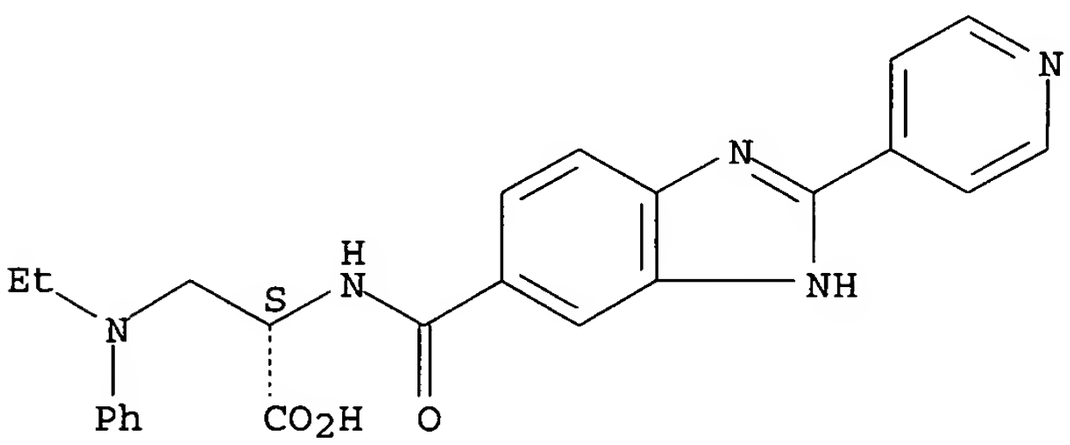


RN 316833-28-0 HCAPLUS
CN L-Alanine, 3-(ethylphenylamino)-N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]-, mono(trifluoroacetate) (9CI) (CA INDEX NAME)

CM 1

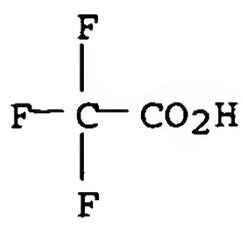
CRN 316833-27-9
CMF C24 H23 N5 O3

Absolute stereochemistry.



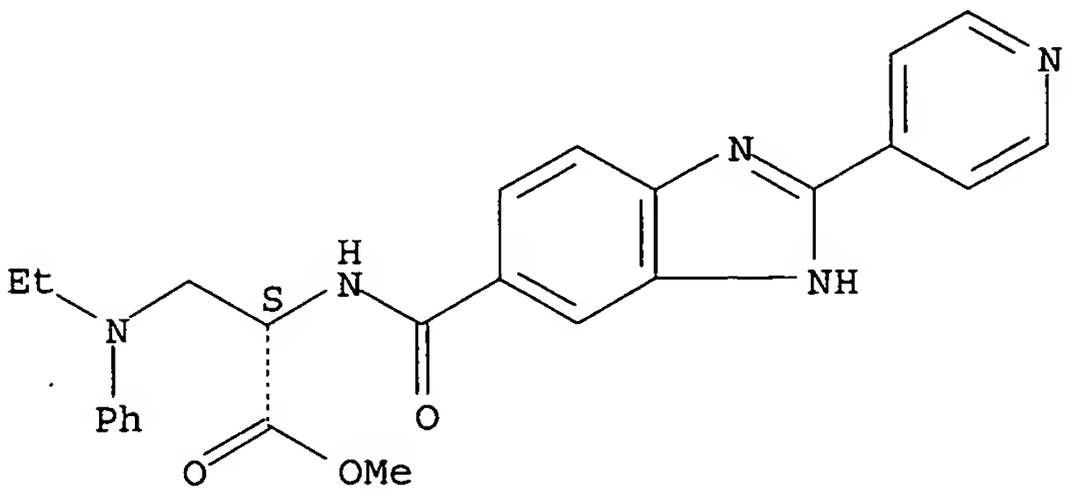
CM 2

CRN 76-05-1
CMF C2 H F3 O2



IT **316833-39-3P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of benzimidazolecarboxylic acid amino acid amides as I κ B **kinase** inhibitors)
RN 316833-39-3 HCAPLUS
CN L-Alanine, 3-(ethylphenylamino)-N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:908698 HCAPLUS
DOCUMENT NUMBER: 134:42443
TITLE: Preparation and use of benzimidazole derivatives for treatment of illness.
INVENTOR(S): Ritzeler, Olaf; Stilz, Hans Ulrich; Neises, Bernhard; Bock, William Jerome, Jr.; Walser, Armin; Flynn, Gary A.
PATENT ASSIGNEE(S): Aventis Pharma Deutschland G.m.b.H., Germany
SOURCE: Ger. Offen., 36 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19928424	A1	20001228	DE 1999-19928424	19990623
CA 2377085	AA	20010104	CA 2000-2377085	20000609
WO 2001000610	A1	20010104	WO 2000-EP5340	20000609

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SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA,
ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,
CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

BR	2000012450	A	20020402	BR 2000-12450	20000609
EP	1194425	A1	20020410	EP 2000-938780	20000609
EP	1194425	B1	20050810		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO

JP	2003503400	T2	20030128	JP 2001-507019	20000609
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AT	301651	E	20050815	AT 2000-938780	20000609
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US	6358978	B1	20020319	US 2000-599390	20000622
ZA	2001010127	A	20021105	ZA 2001-10127	20011210
NO	2001006154	A	20020219	NO 2001-6154	20011217
HK	1047582	A1	20050304	HK 2002-108645	20021129

PRIORITY APPLN. INFO.:	DE 1999-19928424	A	19990623
	DE 2000-10006297	A	20000212
	WO 2000-EP5340	W	20000609

OTHER SOURCE(S): MARPAT 134:42443
GI

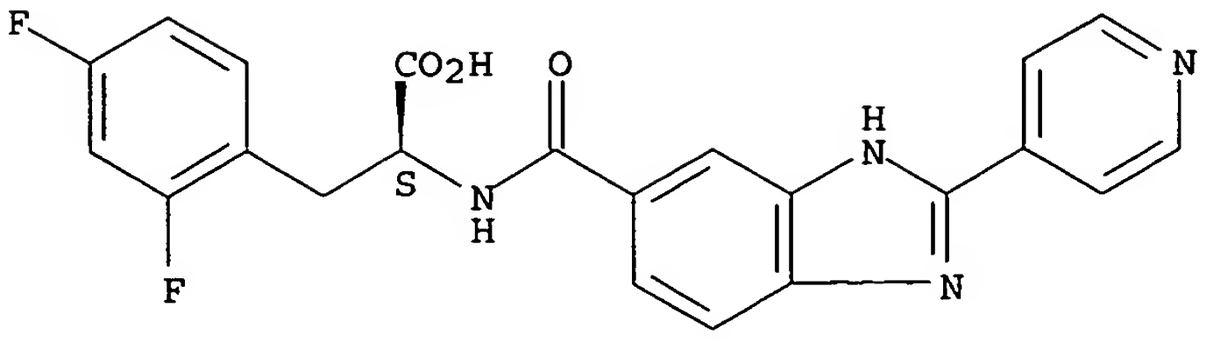
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds., e.g. (I), were prepared (no data) for use in treating diseases which feature an intensified activity by transcription factor NF. **kappa.**B. An example is given of solid-phase synthesis of (II). In in vitro tests, I had IC50 of 1 μM for I κ B-**kinase**, while inhibiting other **kinase** activities (protein **kinases** A and C, and casein **kinase**) 36, 63, and 70%, resp. In the same tests, II showed IC50 of 25 μM for I. **kappa.**B, and inhibited the other **kinases** 24, 7, and 17%, resp.

IT **313064-88-9P 313064-89-0P 313064-90-3P**
313064-91-4P 313064-94-7P 313064-95-8P
313064-97-0P 313064-99-2P 313065-03-1P
313065-04-2P 313065-18-8P 313065-20-2P
313066-07-8P 313066-15-8P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation and use of benzimidazole derivs. for treatment of illness)

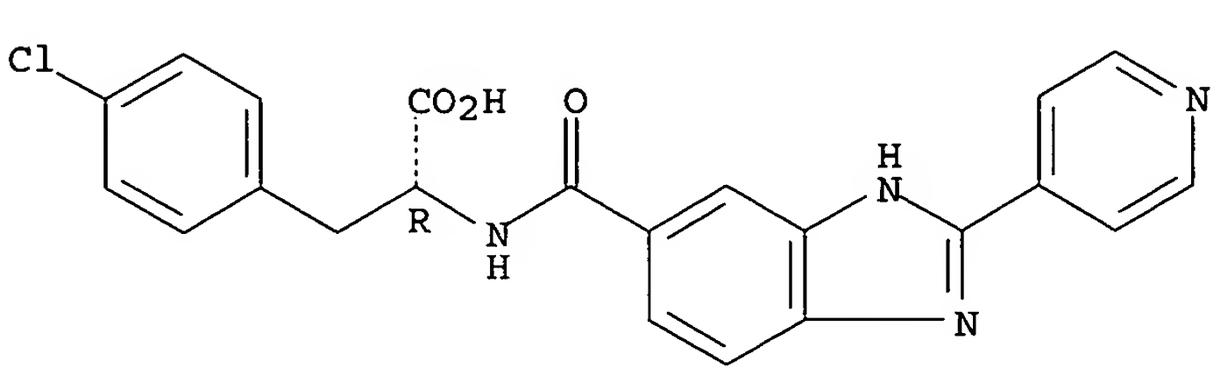
RN 313064-88-9 HCAPLUS
CN L-Phenylalanine, 2,4-difluoro-N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



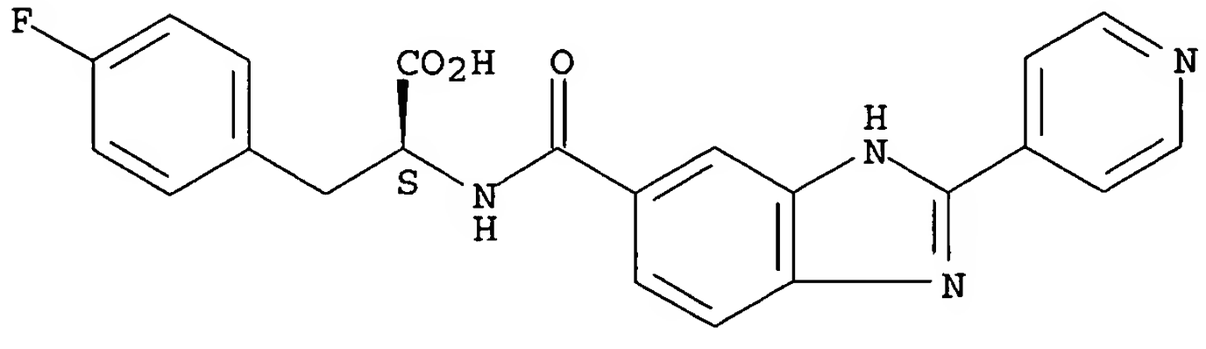
RN 313064-89-0 HCAPLUS
CN D-Phenylalanine, 4-chloro-N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



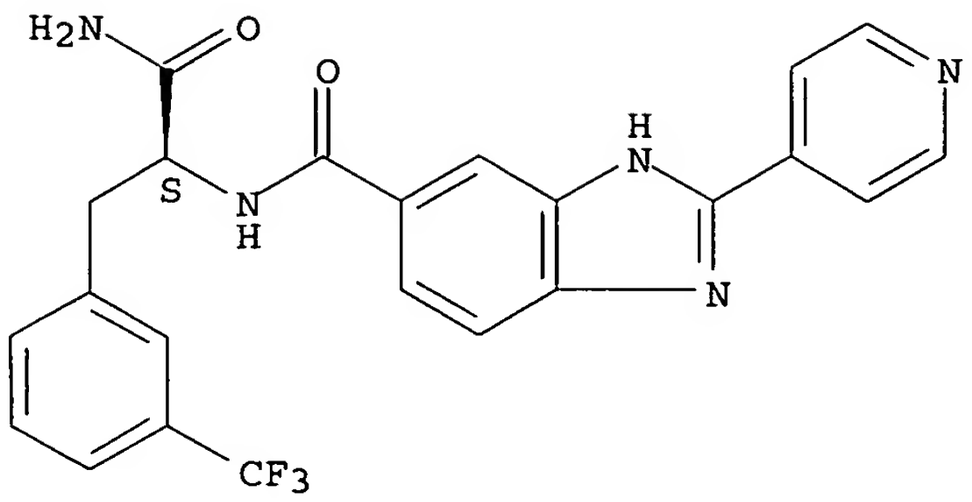
RN 313064-90-3 HCAPLUS
CN L-Phenylalanine, 4-fluoro-N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



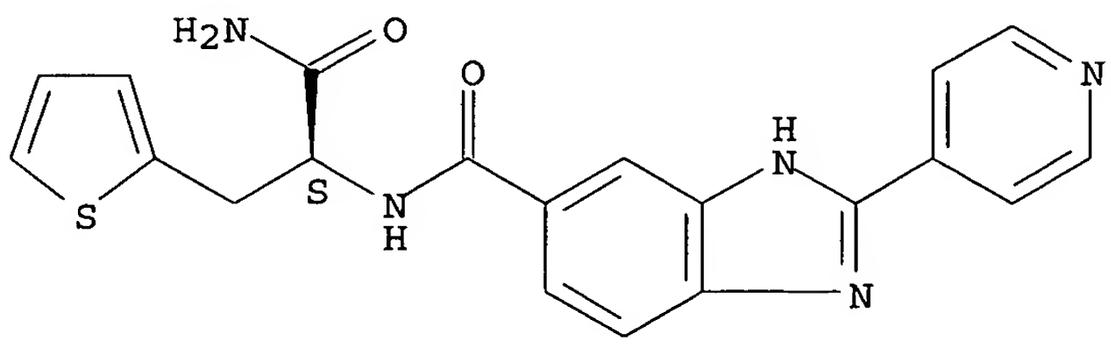
RN 313064-91-4 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-2-amino-2-oxo-1-[[3-(trifluoromethyl)phenyl]methyl]ethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



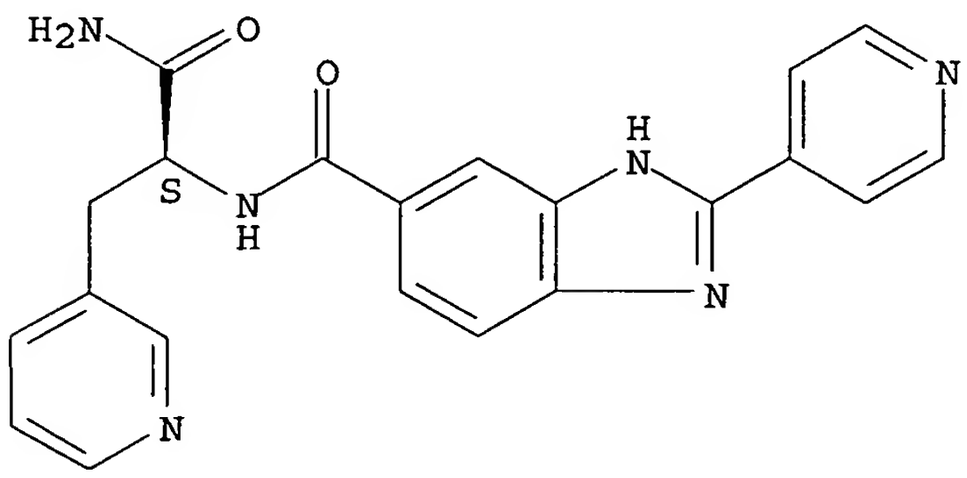
RN 313064-94-7 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-2-amino-2-oxo-1-(2-thienylmethyl)ethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



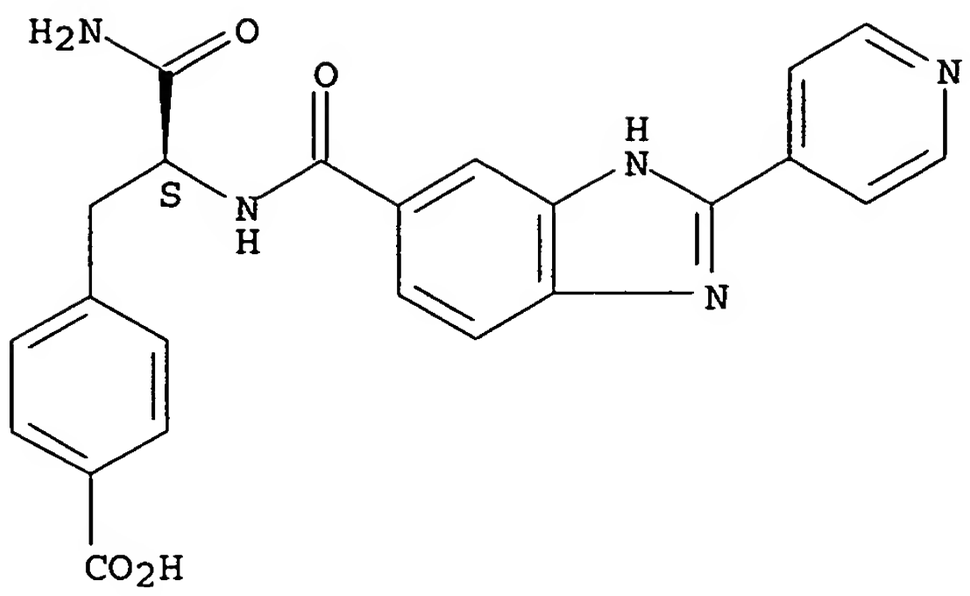
RN 313064-95-8 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-2-amino-2-oxo-1-(3-pyridinylmethyl)ethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



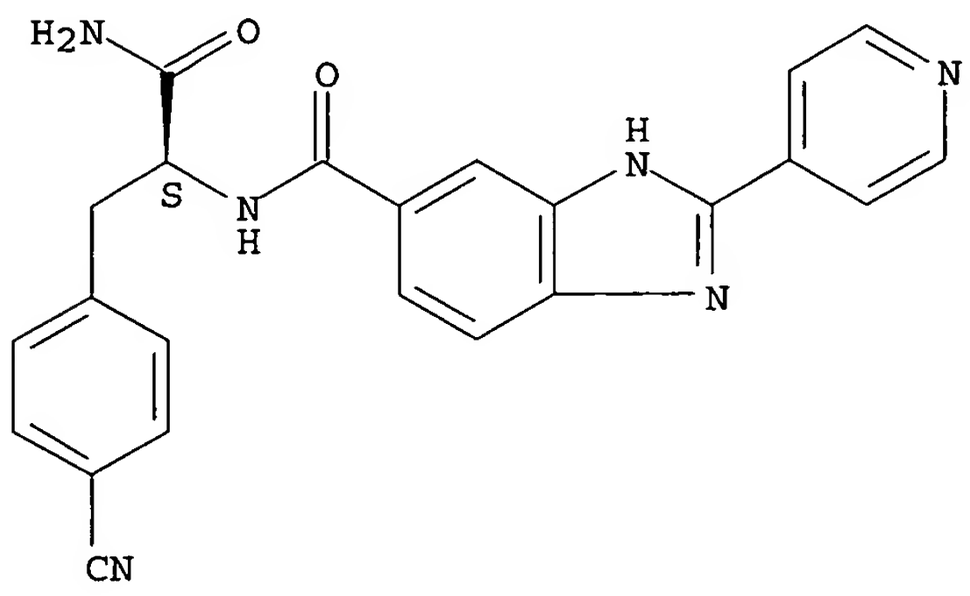
RN 313064-97-0 HCAPLUS
CN Benzoic acid, 4-[(2S)-3-amino-3-oxo-2-[[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]amino]propyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



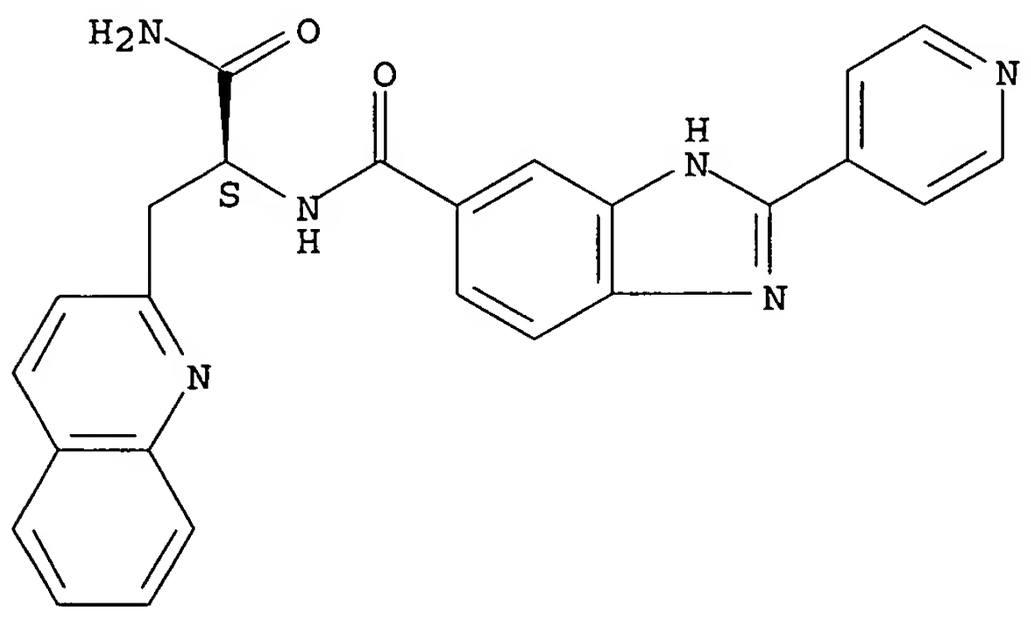
RN 313064-99-2 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-2-amino-1-[(4-cyanophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 313065-03-1 HCAPLUS
CN 2-Quinolinepropanamide, α-[[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]amino]-, (αS)- (9CI) (CA INDEX NAME)

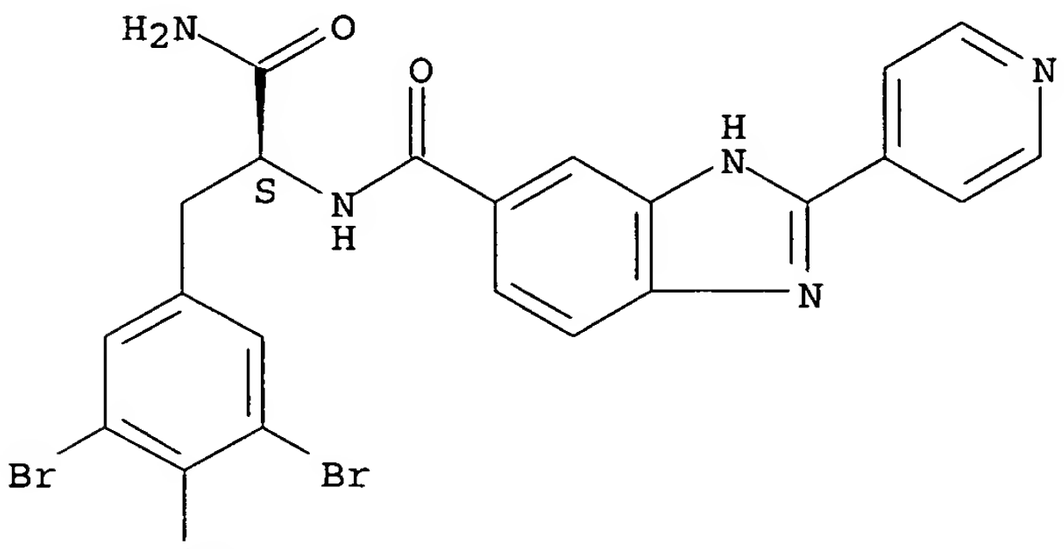
Absolute stereochemistry.



RN 313065-04-2 HCAPLUS

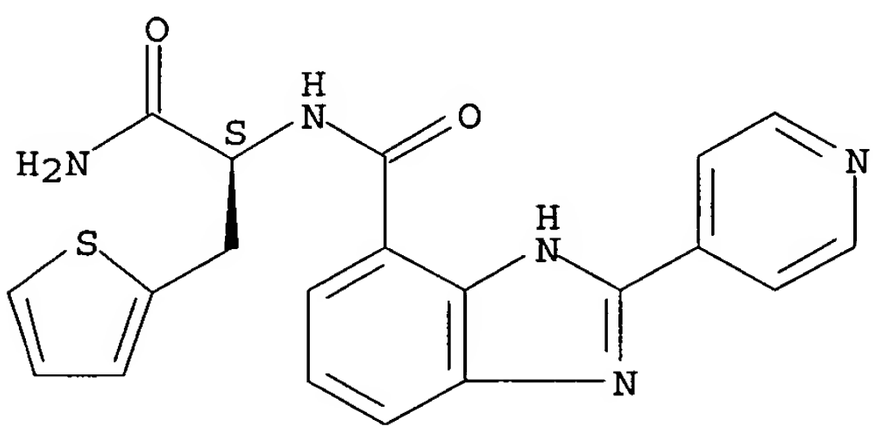
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-2-amino-1-[(3,5-dibromo-4-hydroxyphenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



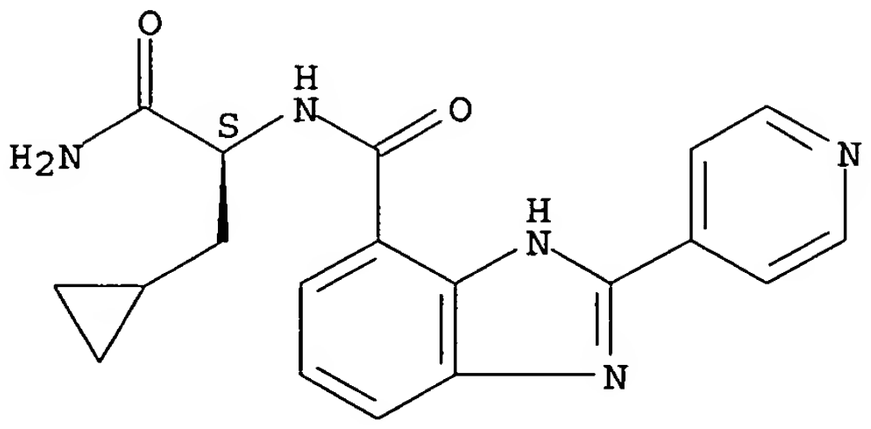
RN 313065-18-8 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-2-amino-2-oxo-1-(2-thienylmethyl)ethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



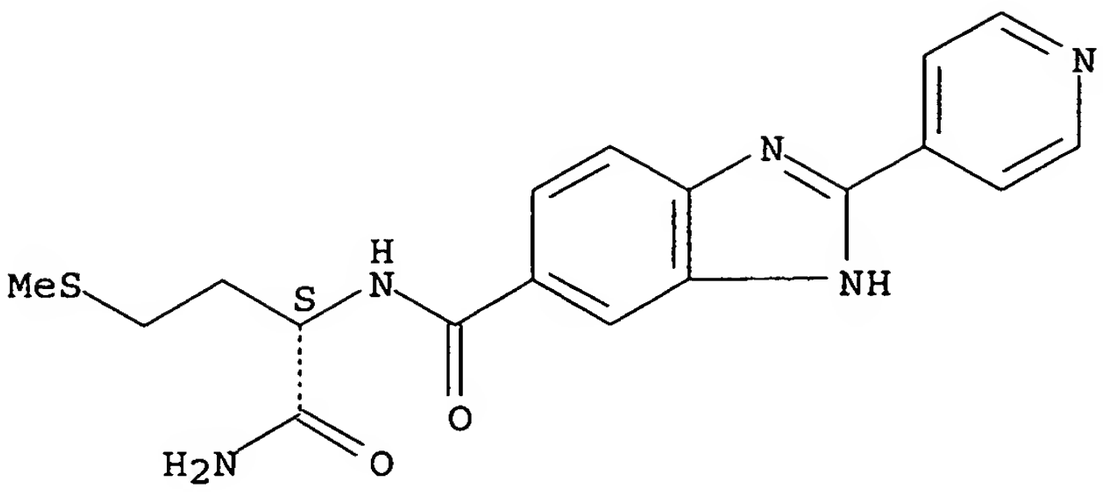
RN 313065-20-2 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-2-amino-1-(cyclopropylmethyl)-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 313066-07-8 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-1-(aminocarbonyl)-3-(methylthio)propyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 313066-15-8 HCAPLUS
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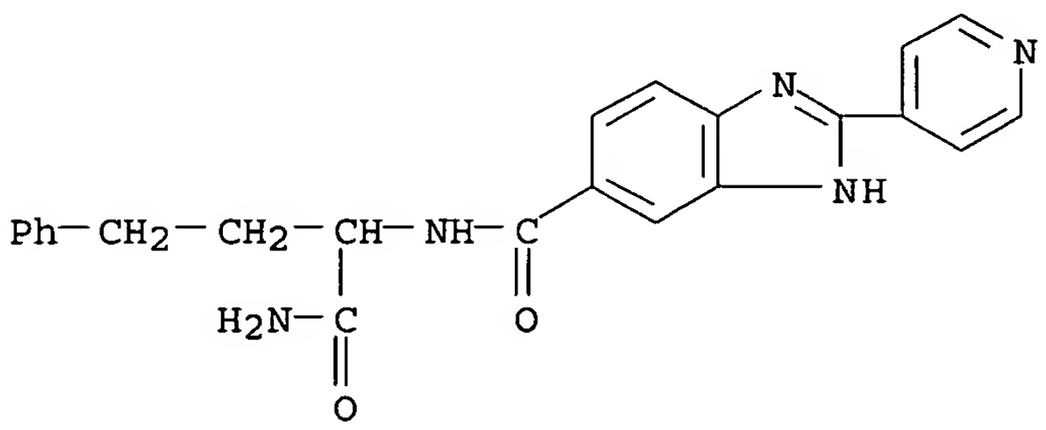

IT **313064-84-5P 313064-85-6P 313064-86-7P**
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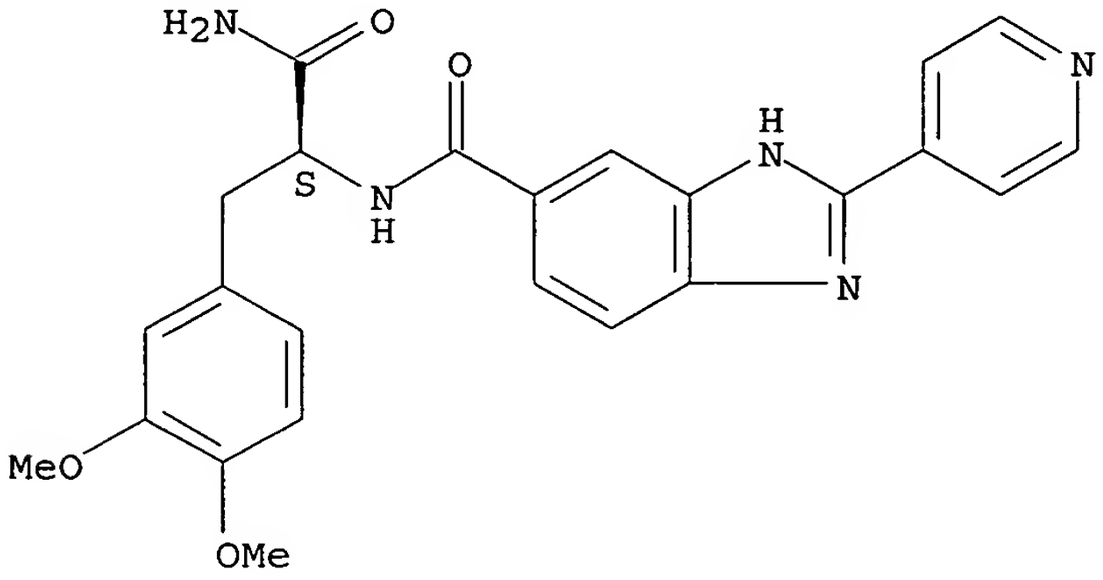
313066-12-5P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation and use of benzimidazole derivs. for treatment of illness)

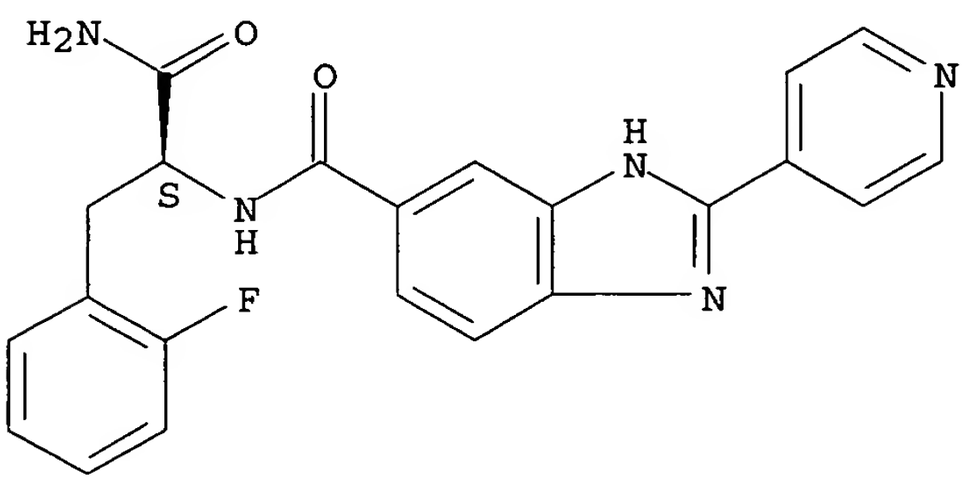
RN 313064-84-5 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-2-amino-1-[(3,4-dimethoxyphenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



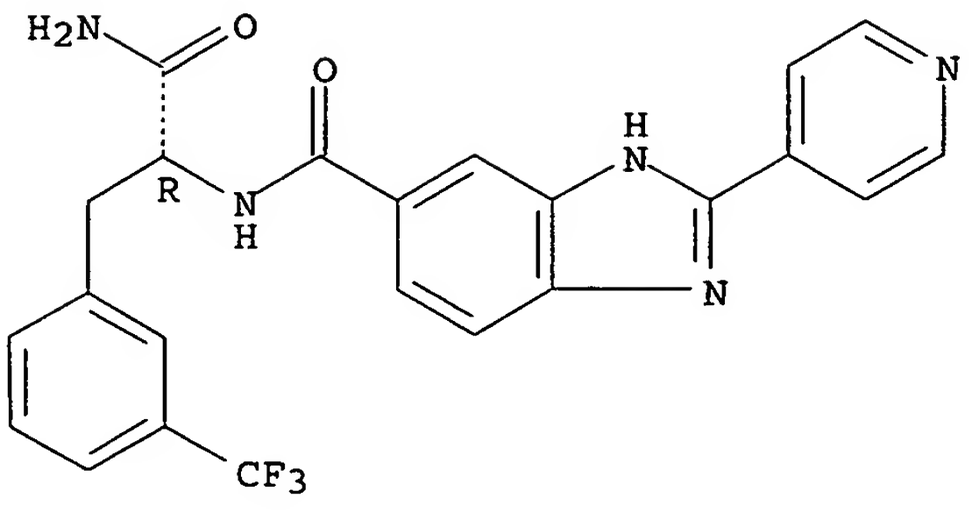
RN 313064-85-6 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-2-amino-1-[(2-fluorophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



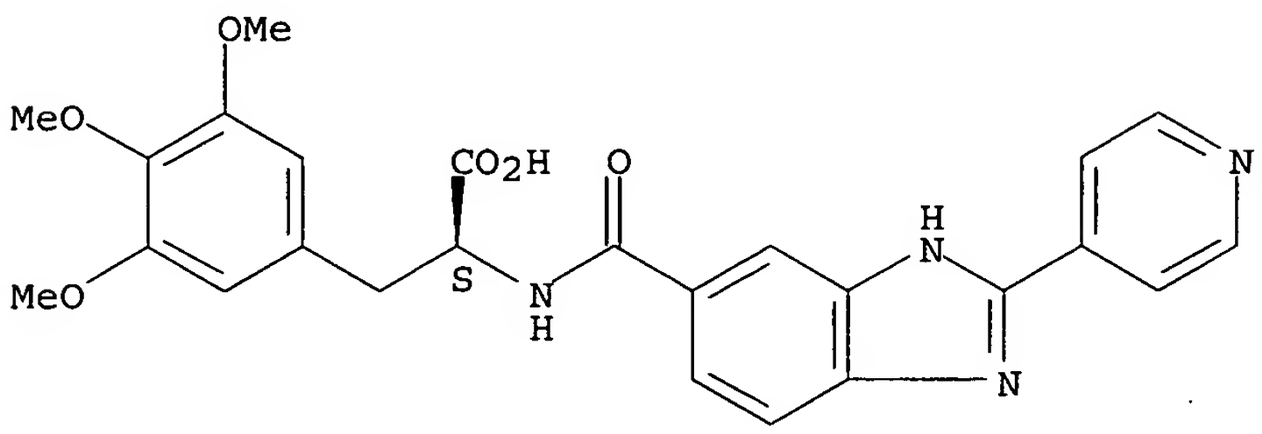
RN 313064-86-7 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1R)-2-amino-2-oxo-1-[[3-(trifluoromethyl)phenyl]methyl]ethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



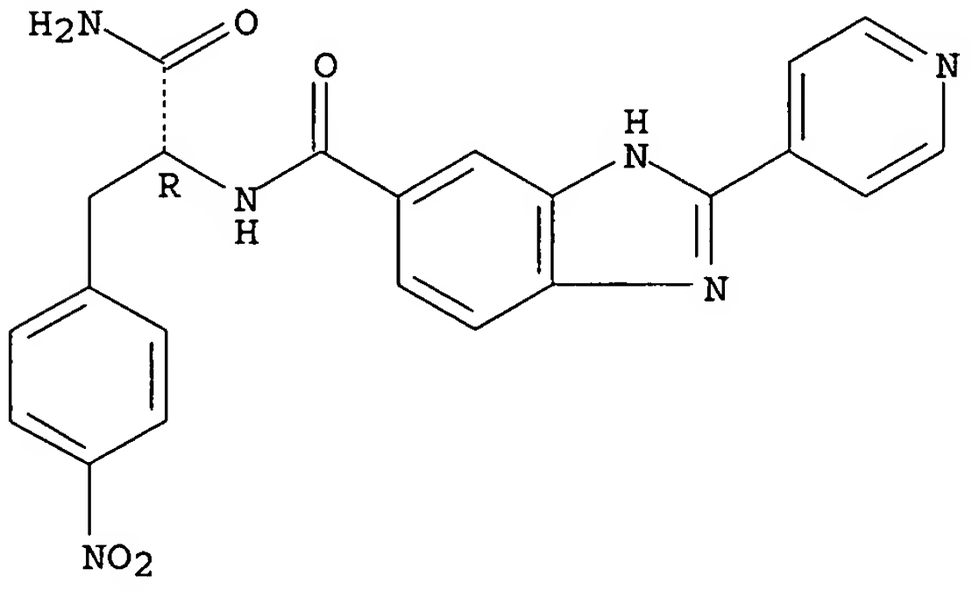
RN 313064-87-8 HCAPLUS
CN L-Tyrosine, 3,5-dimethoxy-O-methyl-N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

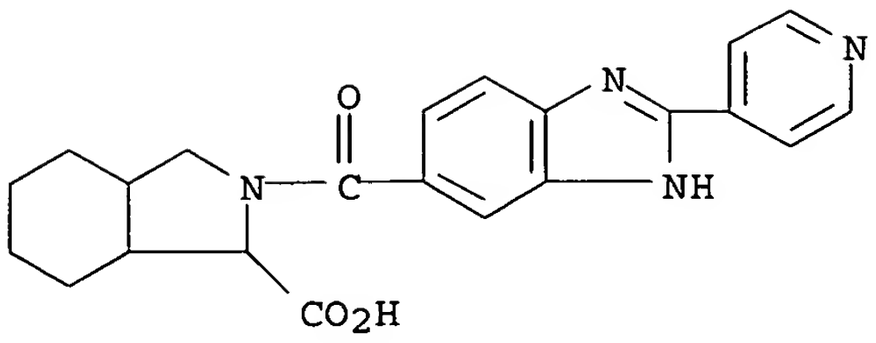


RN 313064-92-5 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1R)-2-amino-1-[(4-nitrophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

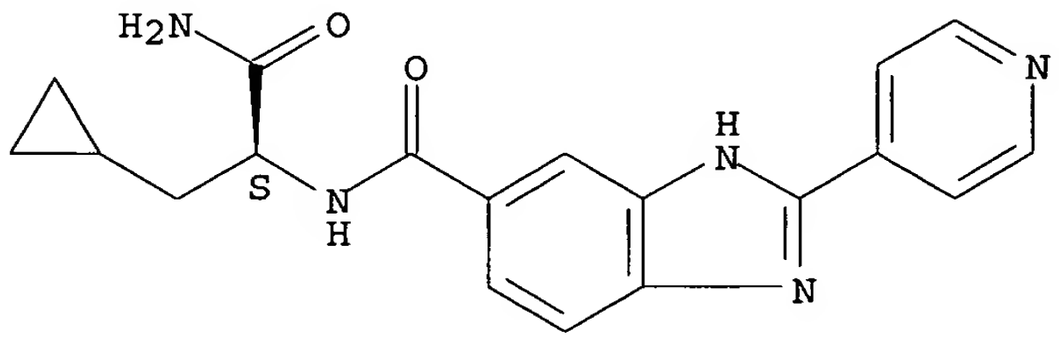


RN 313064-93-6 HCAPLUS
CN 1H-Isoindole-1-carboxylic acid, octahydro-2-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]- (9CI) (CA INDEX NAME)



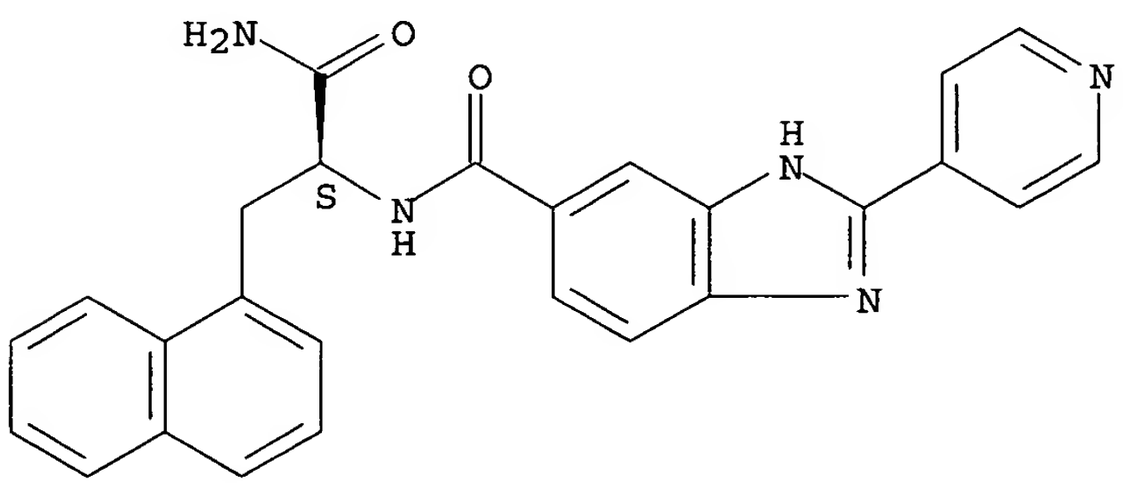
RN 313064-96-9 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-2-amino-1-(cyclopropylmethyl)-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



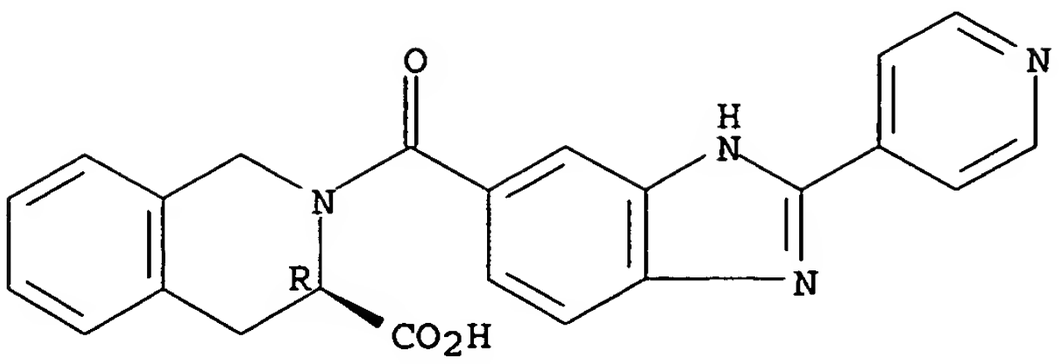
RN 313064-98-1 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-2-amino-1-(1-naphthalenylmethyl)-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



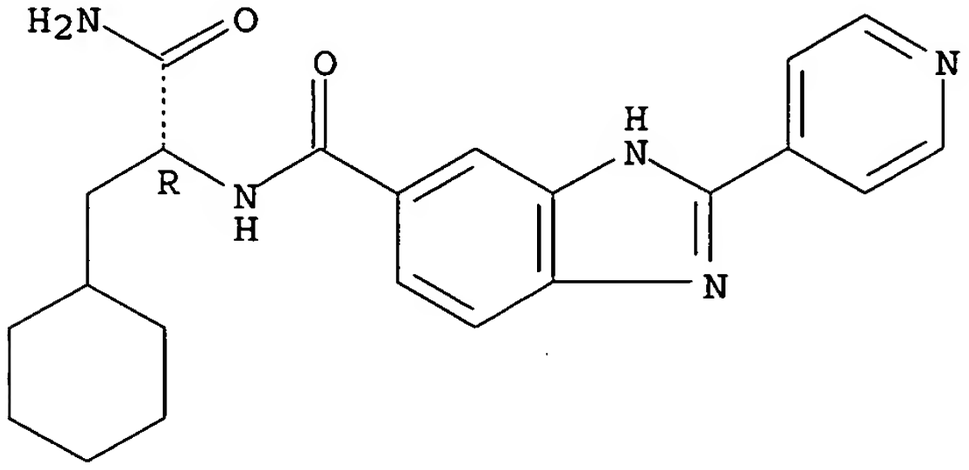
RN 313065-00-8 HCAPLUS
CN 3-Isoquinolinecarboxylic acid, 1,2,3,4-tetrahydro-2-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]-, (3R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

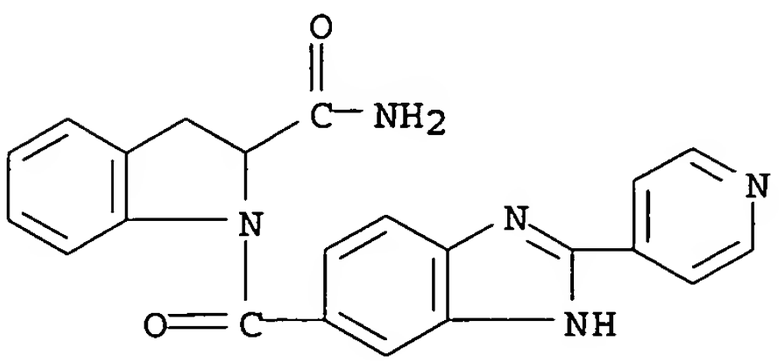


RN 313065-01-9 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1R)-2-amino-1-(cyclohexylmethyl)-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

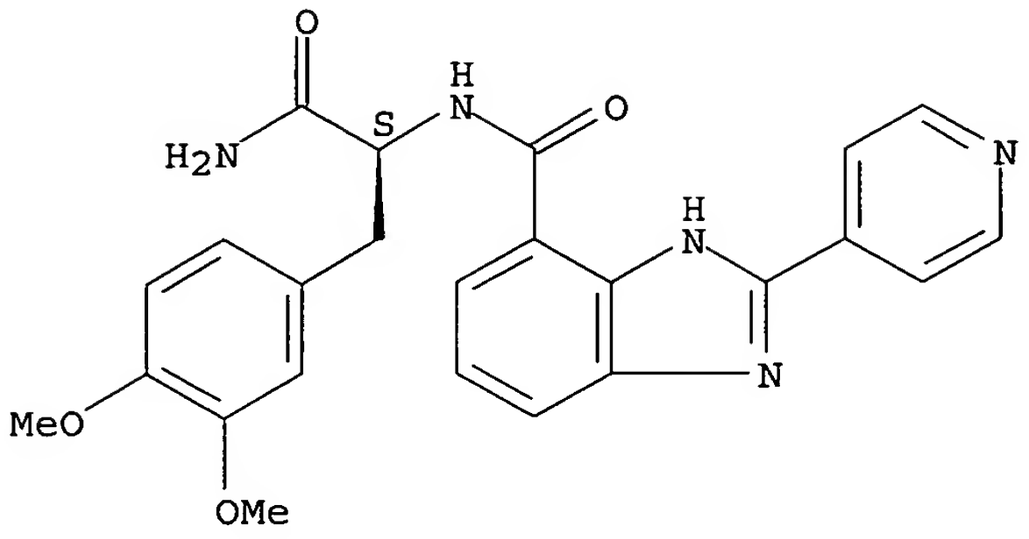


RN 313065-02-0 HCAPLUS
CN 1H-Indole-2-carboxamide, 2,3-dihydro-1-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]- (9CI) (CA INDEX NAME)

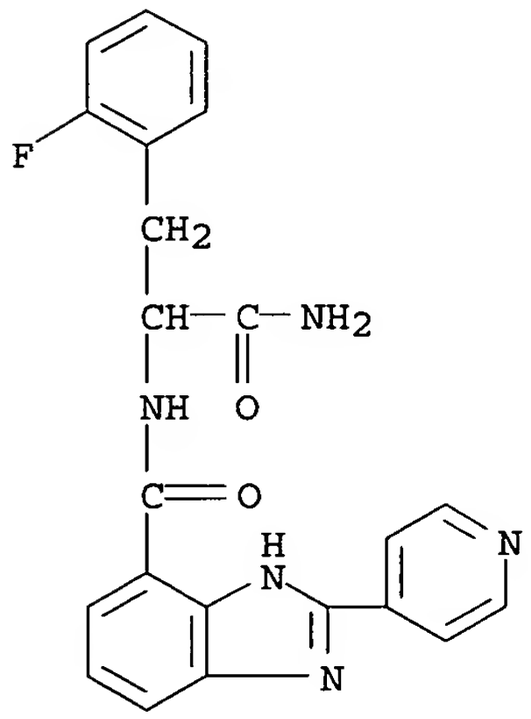


RN 313065-05-3 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-2-amino-1-[(3,4-dimethoxyphenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

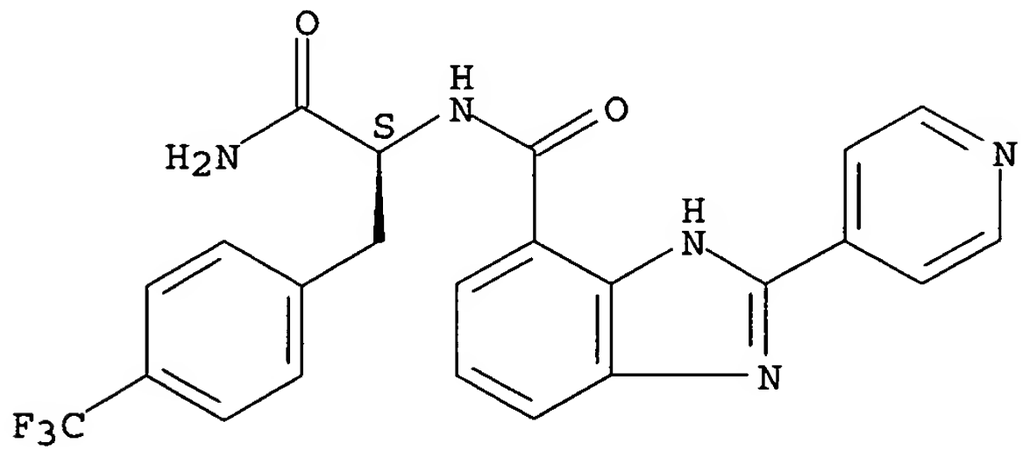


RN 313065-06-4 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[2-amino-1-[(2-fluorophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)



RN 313065-07-5 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-2-amino-2-oxo-1-[[4-(trifluoromethyl)phenyl]methyl]ethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

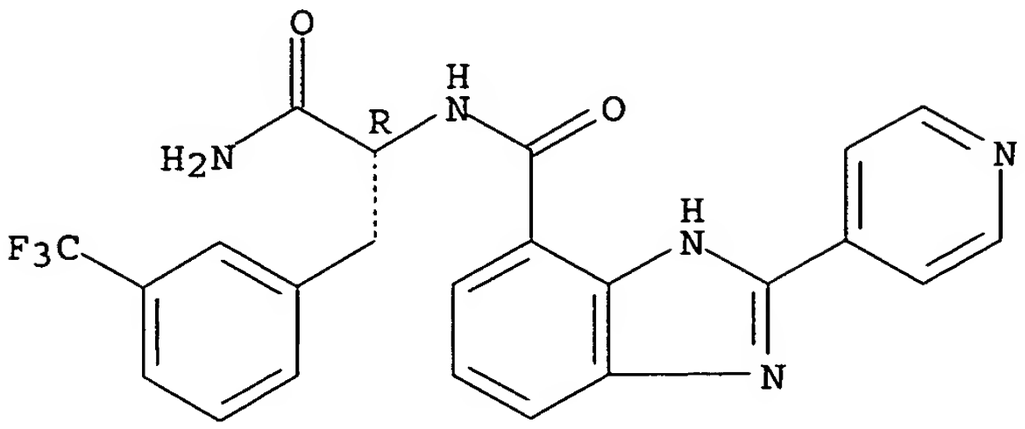
Absolute stereochemistry.



RN 313065-08-6 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1R)-2-amino-2-oxo-1-[[3-(trifluoromethyl)phenyl]methyl]ethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX

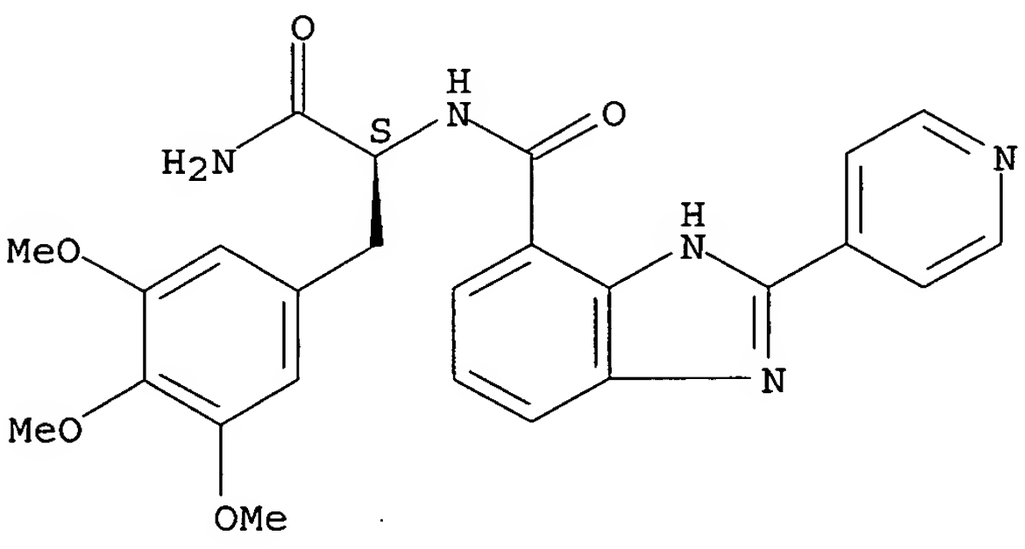
NAME)

Absolute stereochemistry.



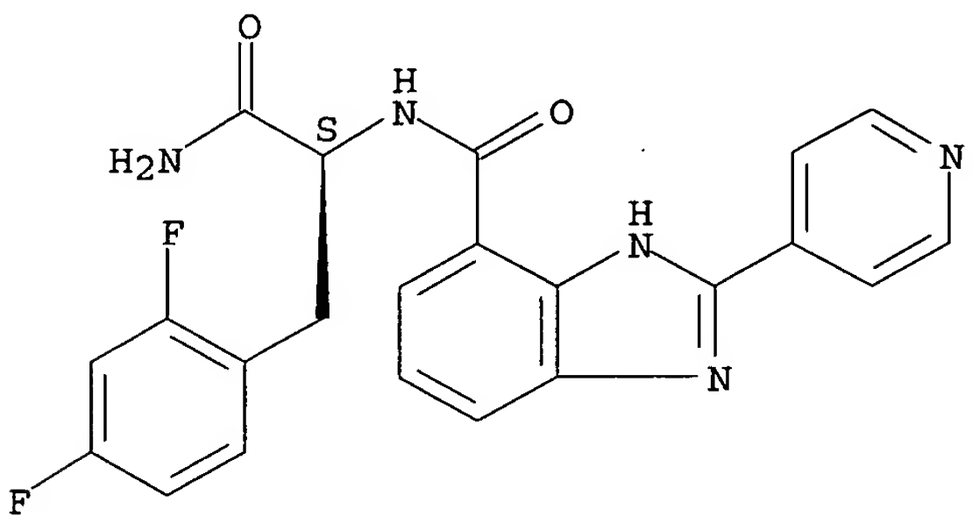
RN 313065-09-7 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-2-amino-2-oxo-1-[(3,4,5-trimethoxyphenyl)methyl]ethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



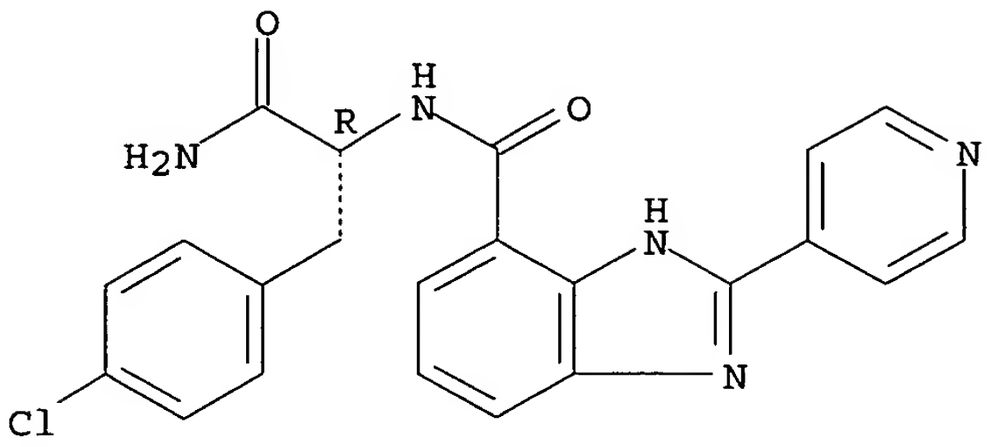
RN 313065-10-0 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-2-amino-1-[(2,4-difluorophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



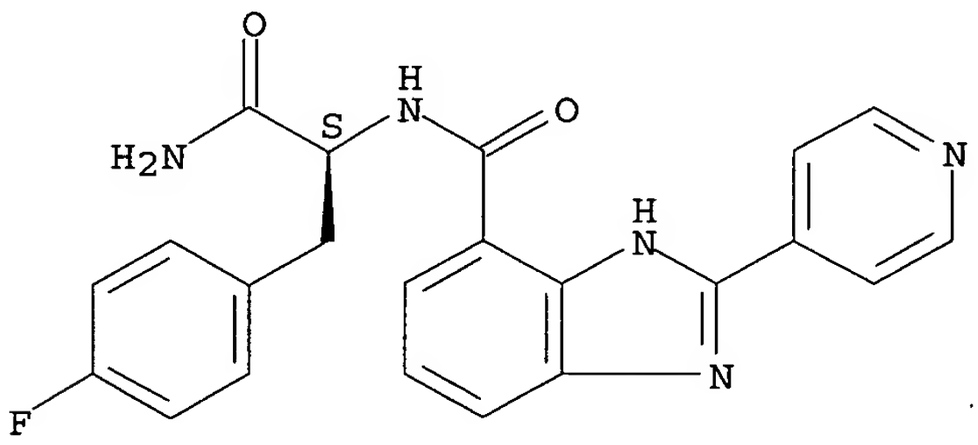
RN 313065-11-1 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1R)-2-amino-1-[(4-chlorophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



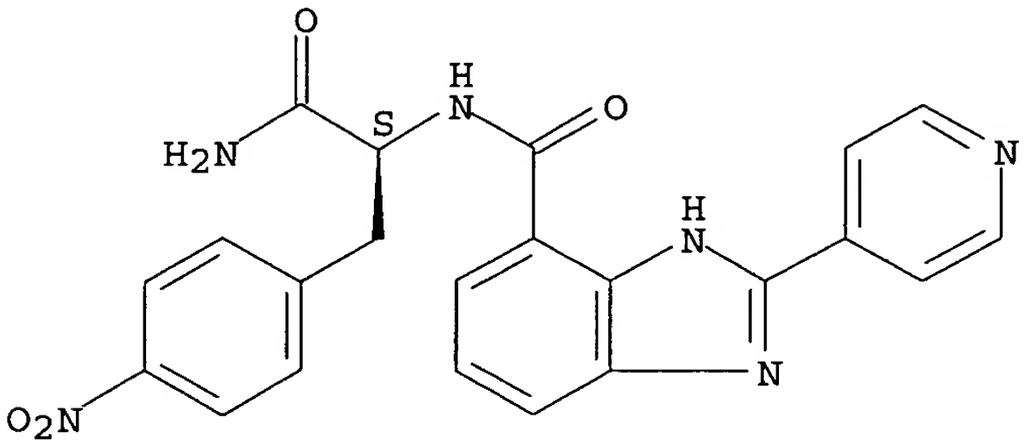
RN 313065-12-2 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-2-amino-1-[(4-fluorophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

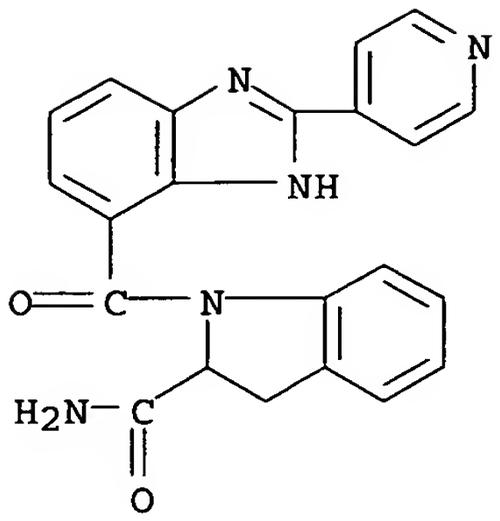


RN 313065-13-3 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-2-amino-1-[(4-nitrophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

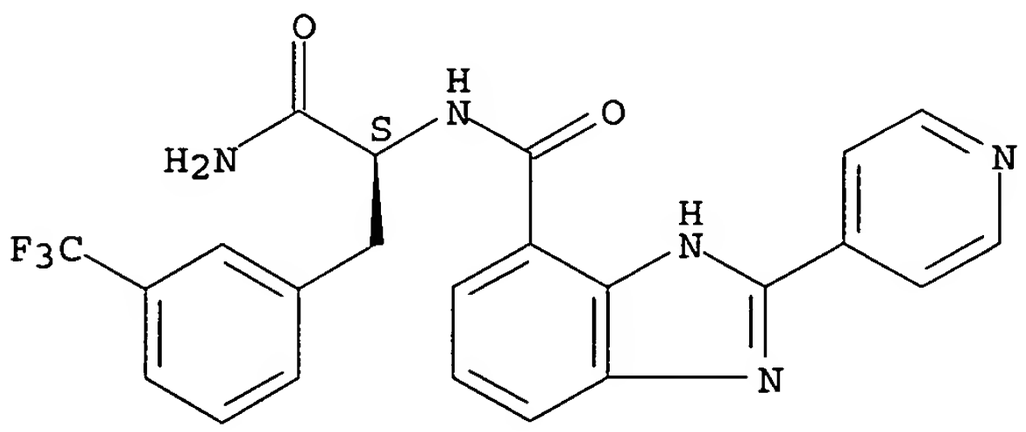


RN 313065-14-4 HCAPLUS
CN 1H-Indole-2-carboxamide, 2,3-dihydro-1-[[2-(4-pyridinyl)-1H-benzimidazol-4-yl]carbonyl]- (9CI) (CA INDEX NAME)



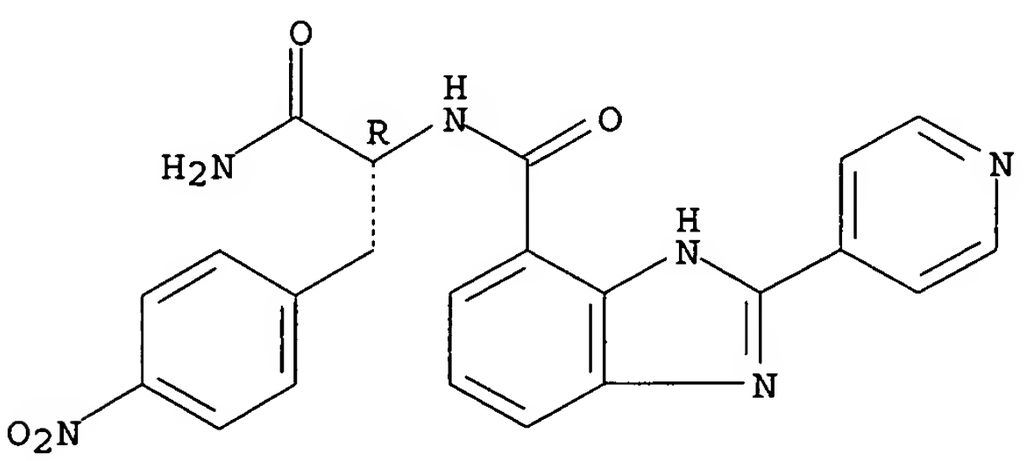
RN 313065-15-5 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-2-amino-2-oxo-1-[[3-(trifluoromethyl)phenyl]methyl]ethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

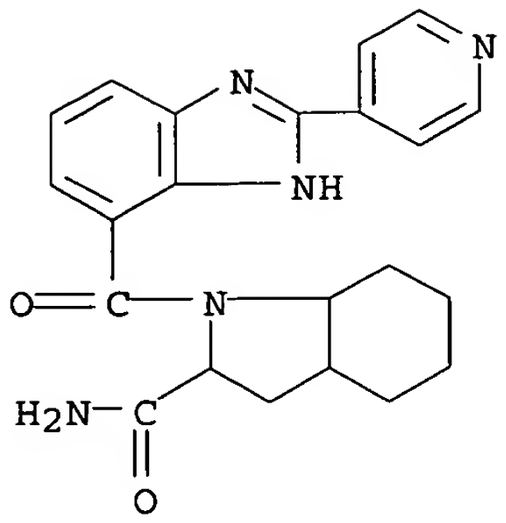


RN 313065-16-6 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1R)-2-amino-1-[(4-nitrophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

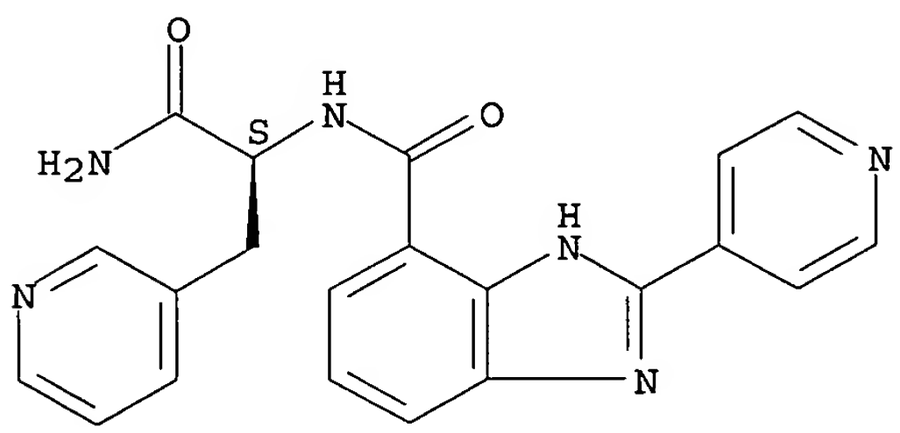


RN 313065-17-7 HCAPLUS
CN 1H-Indole-2-carboxamide, octahydro-1-[[2-(4-pyridinyl)-1H-benzimidazol-4-yl]carbonyl]- (9CI) (CA INDEX NAME)



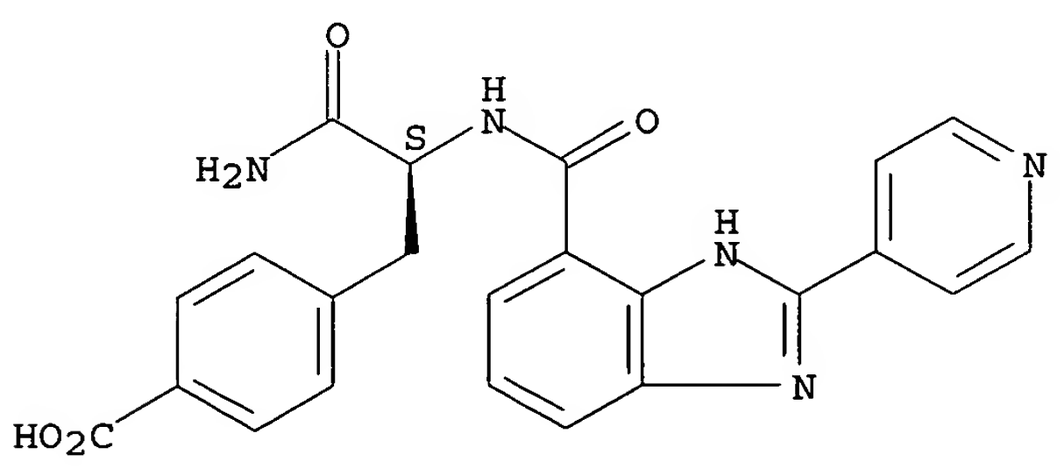
RN 313065-19-9 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-2-amino-2-oxo-1-(3-pyridinylmethyl)ethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



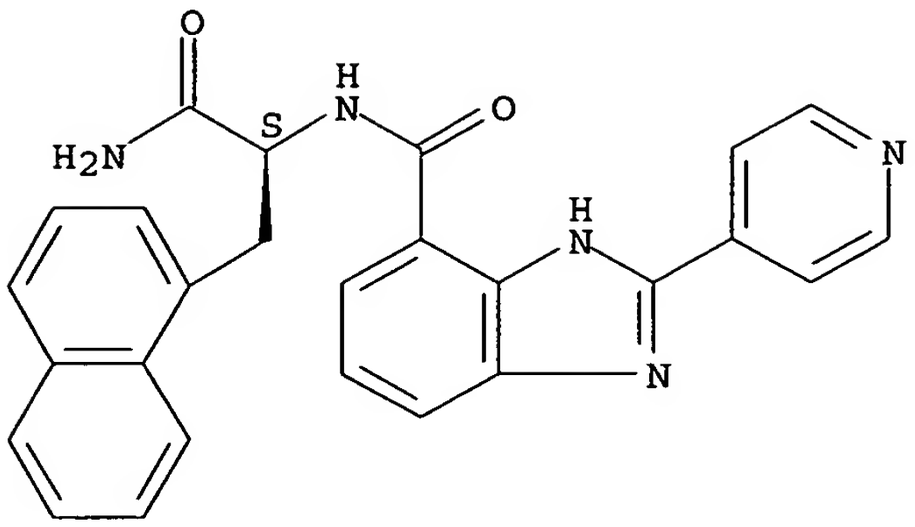
RN 313065-21-3 HCAPLUS
CN Benzoic acid, 4-[(2S)-3-amino-3-oxo-2-[[[2-(4-pyridinyl)-1H-benzimidazol-4-yl]carbonyl]amino]propyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



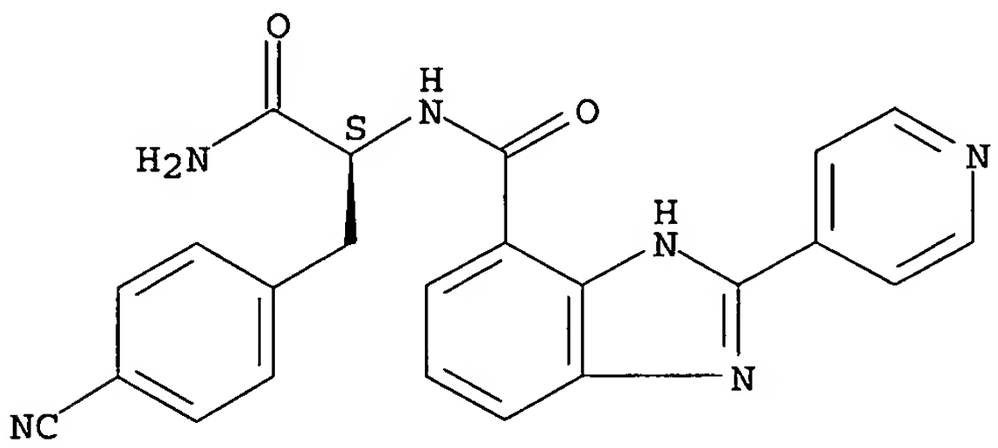
RN 313065-22-4 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-2-amino-1-(1-naphthalenylmethyl)-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



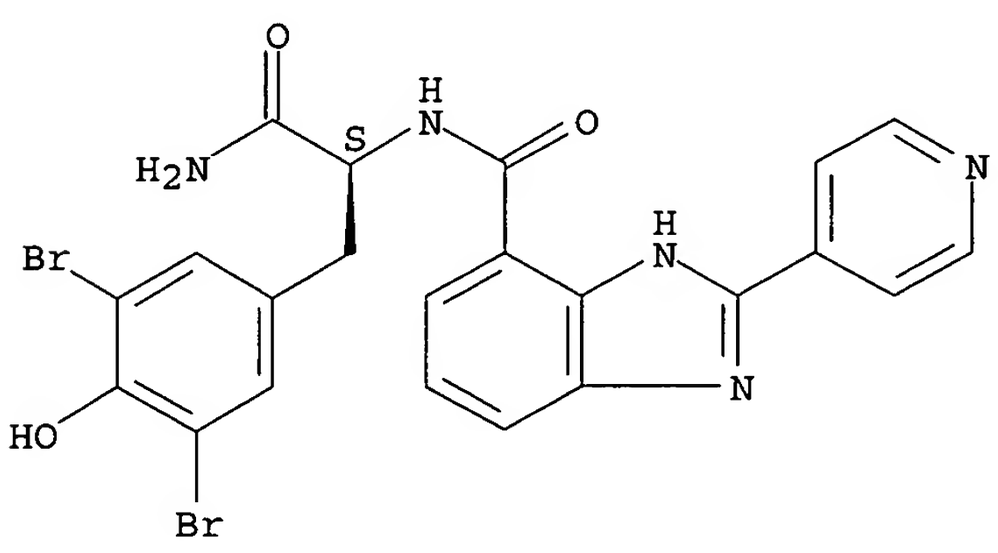
RN 313065-24-6 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-2-amino-1-[(4-cyanophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



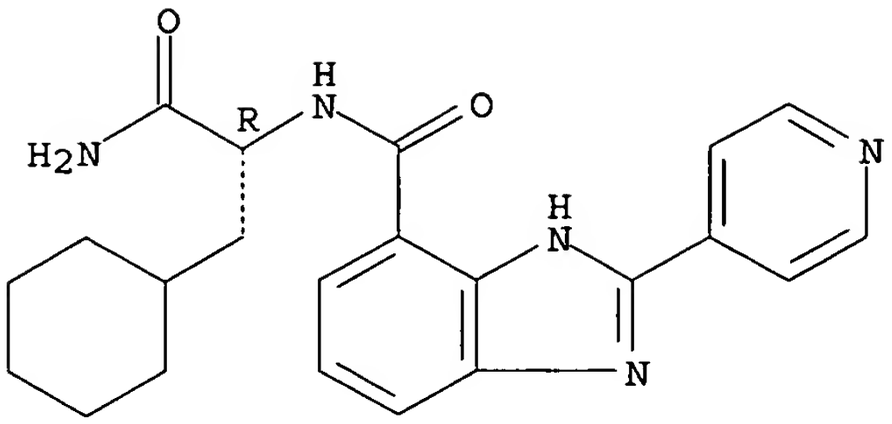
RN 313065-25-7 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-2-amino-1-[(3,5-dibromo-4-hydroxyphenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



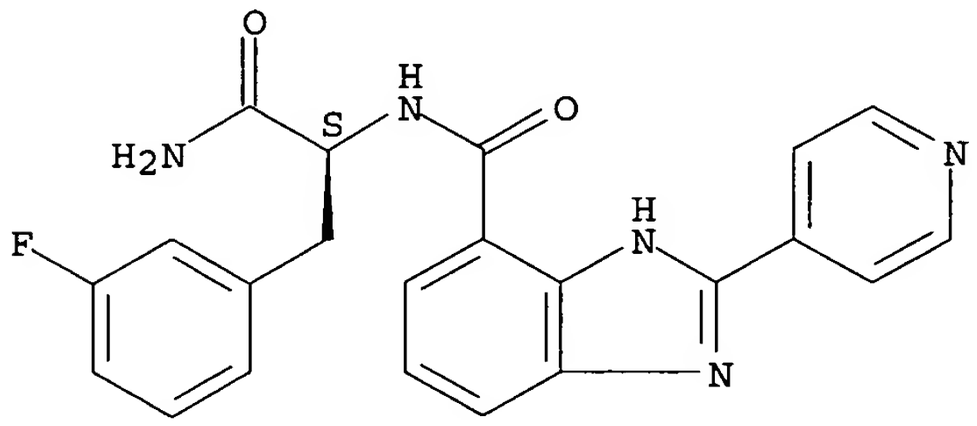
RN 313065-26-8 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1R)-2-amino-1-(cyclohexylmethyl)-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



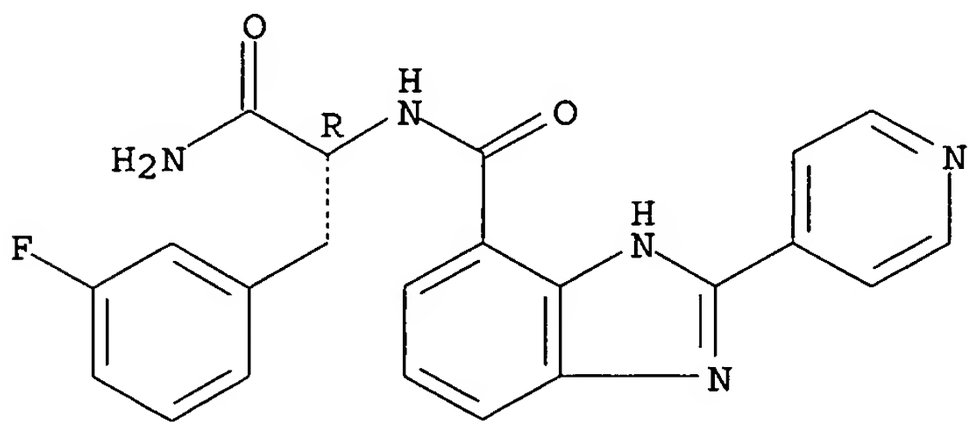
RN 313065-27-9 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-2-amino-1-[(3-fluorophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



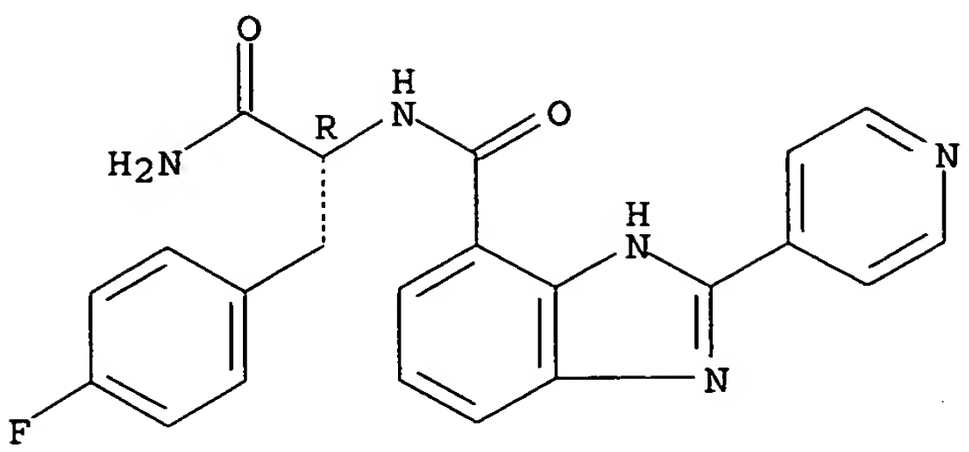
RN 313065-28-0 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1R)-2-amino-1-[(3-fluorophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



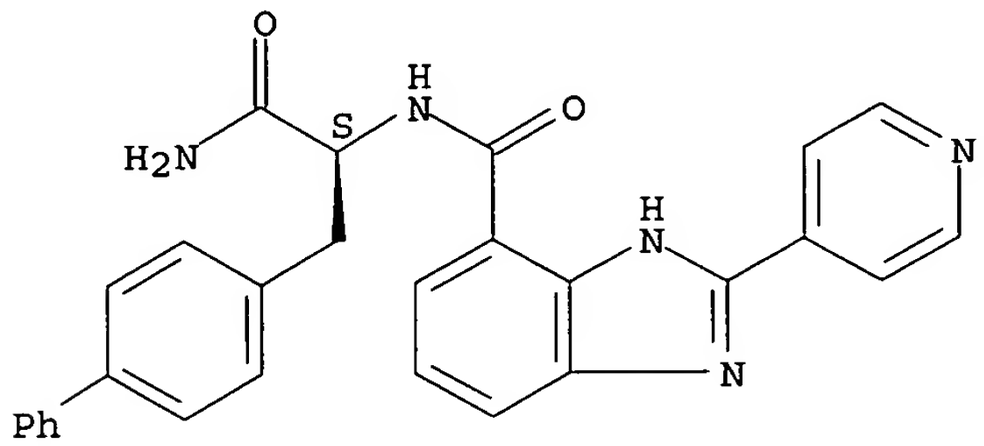
RN 313065-29-1 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1R)-2-amino-1-[(4-fluorophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

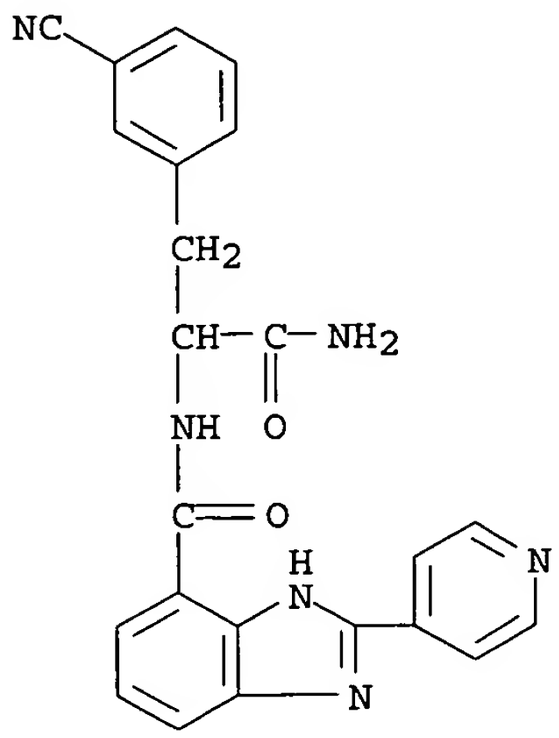


RN 313065-30-4 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-2-amino-1-([1,1'-biphenyl]-4-ylmethyl)-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

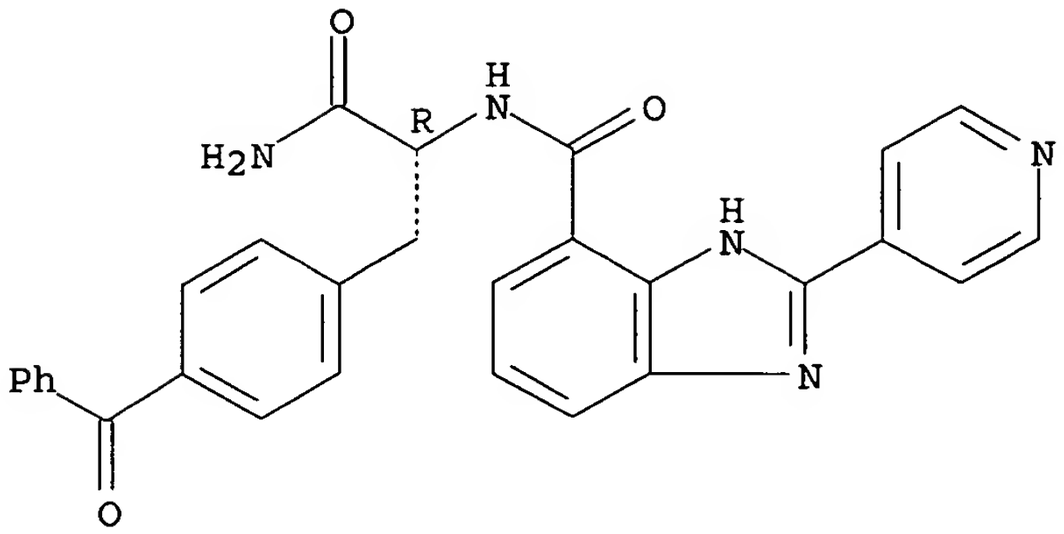


RN 313065-31-5 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[2-amino-1-[(3-cyanophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)



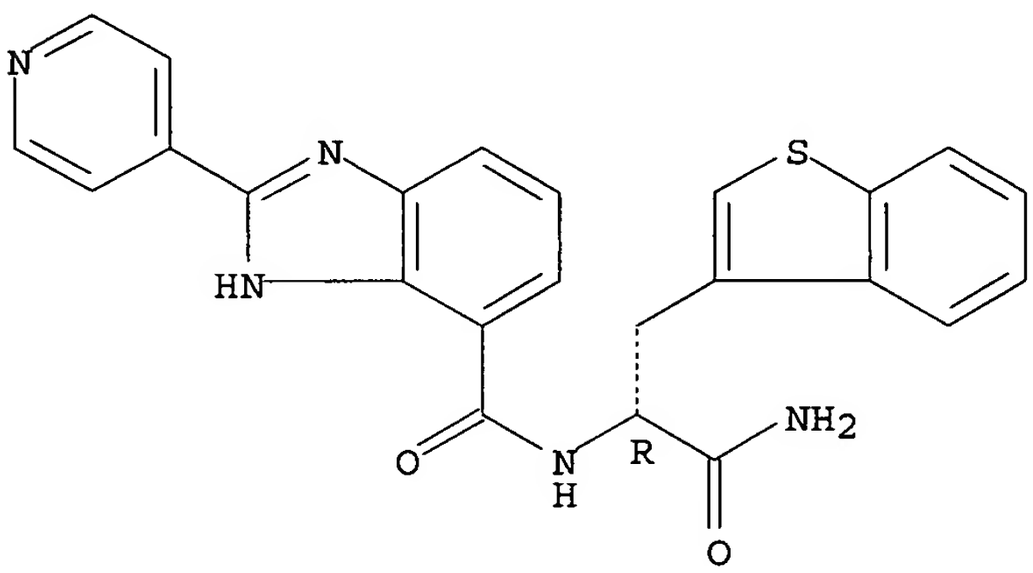
RN 313065-32-6 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1R)-2-amino-1-[(4-benzoylphenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

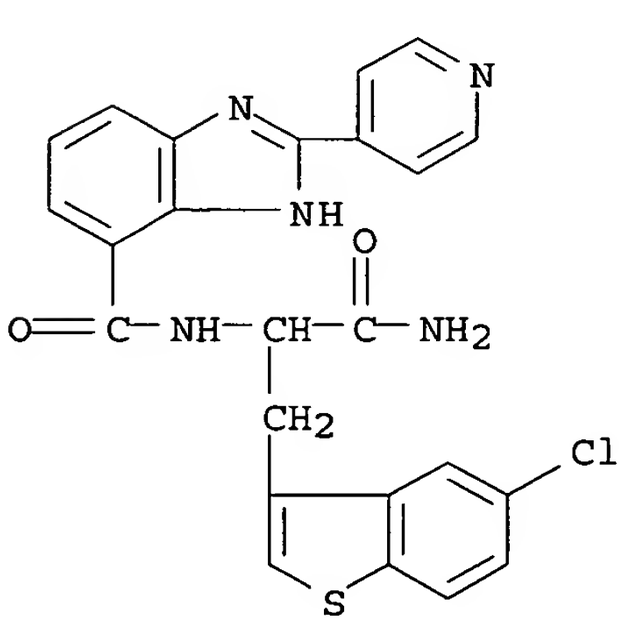


RN 313065-33-7 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1R)-2-amino-1-(benzo[b]thien-3-ylmethyl)-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

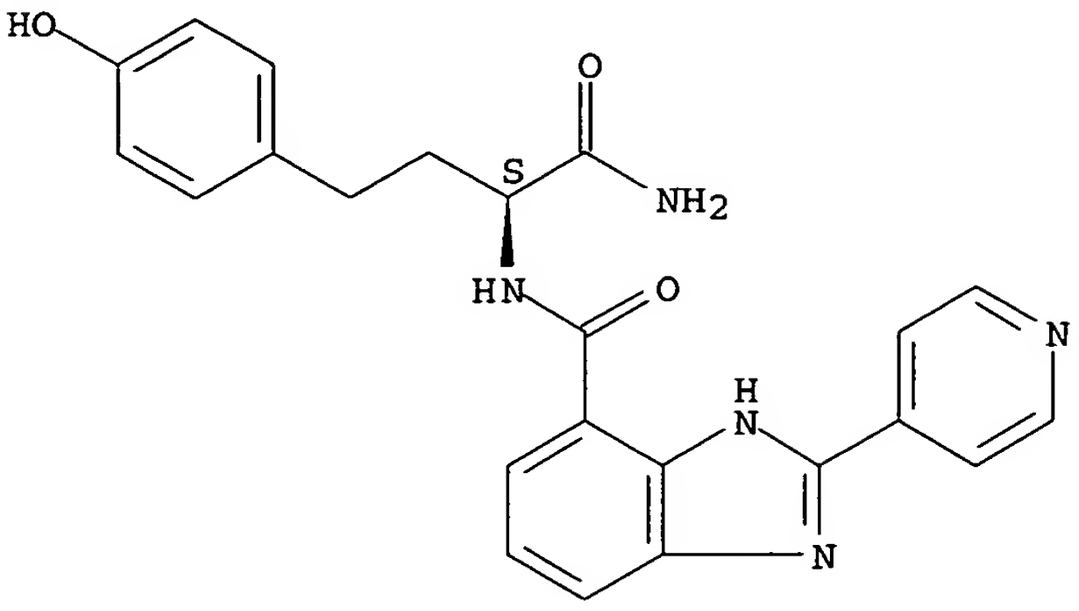


RN 313065-34-8 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[2-amino-1-[(5-chlorobenzo[b]thien-3-yl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)



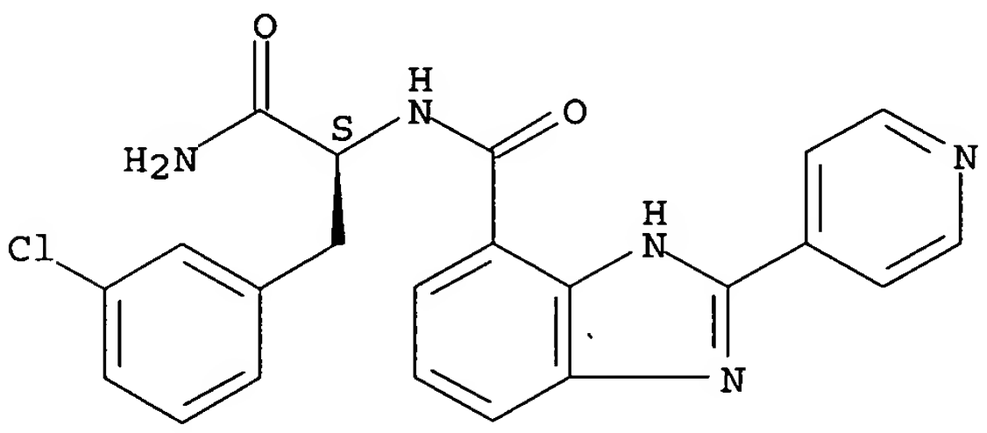
RN 313065-35-9 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-1-(aminocarbonyl)-3-(4-hydroxyphenyl)propyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



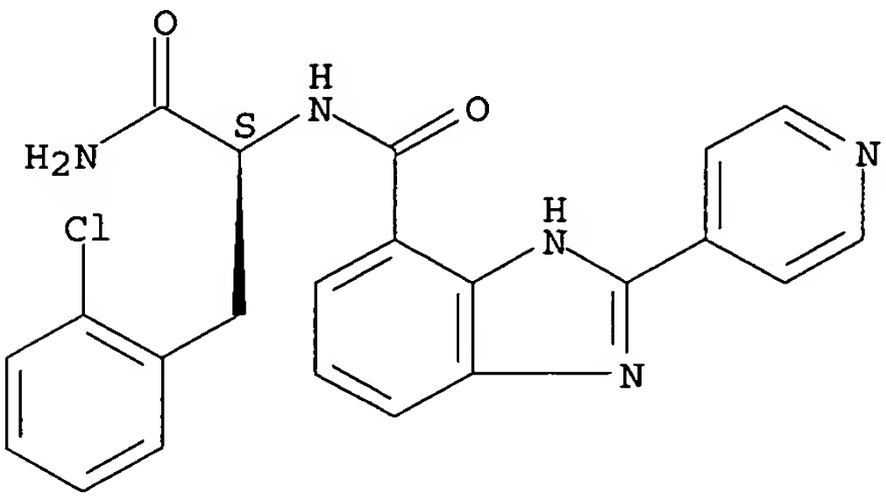
RN 313065-36-0 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-2-amino-1-[(3-chlorophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



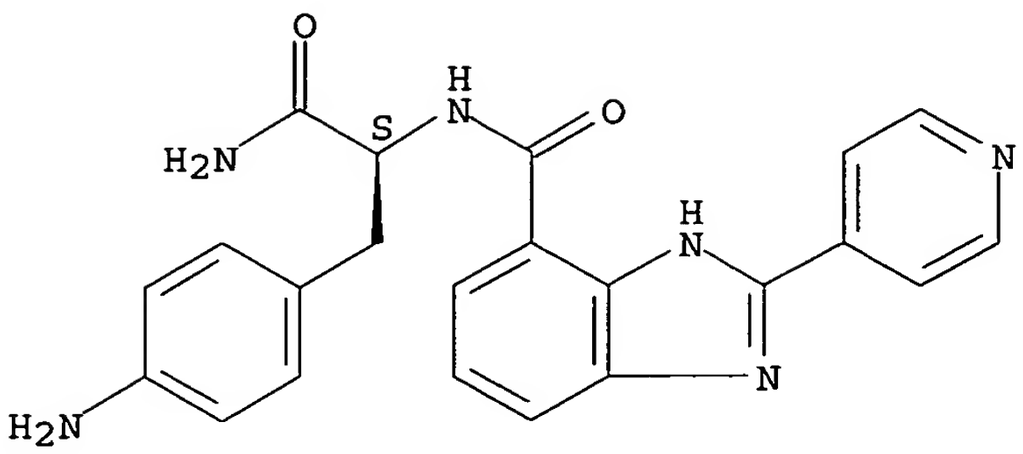
RN 313065-37-1 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-2-amino-1-[(2-chlorophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



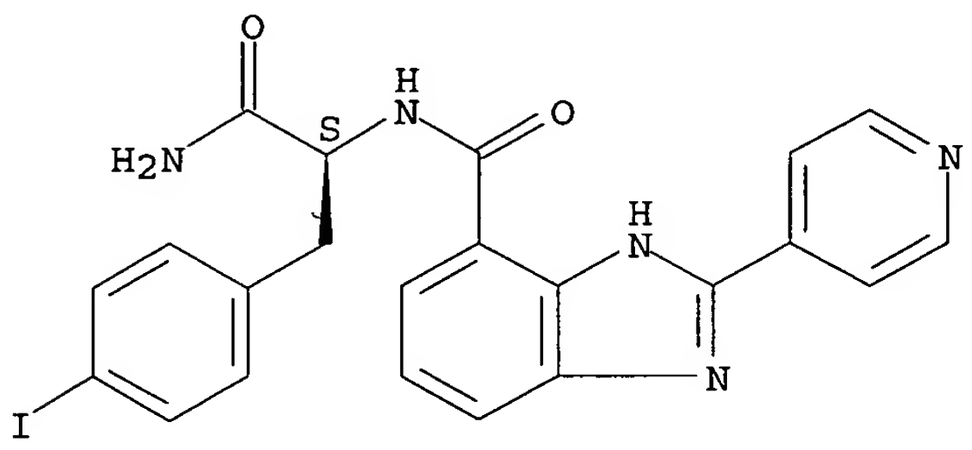
RN 313065-38-2 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-2-amino-1-[(4-aminophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



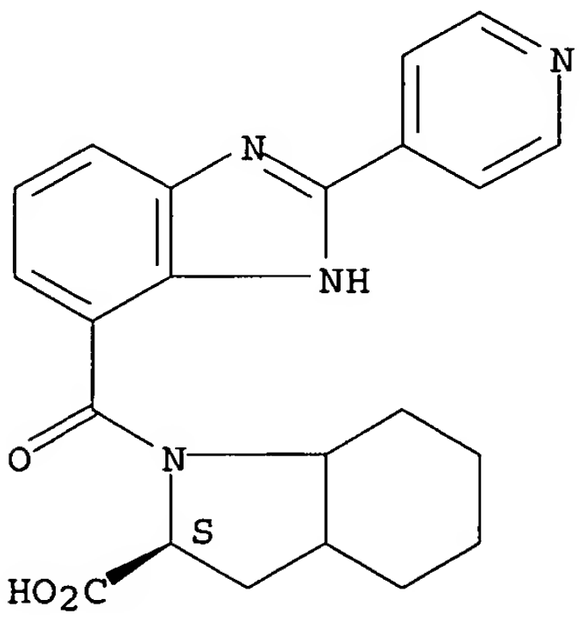
RN 313065-39-3 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-2-amino-1-[(4-iodophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

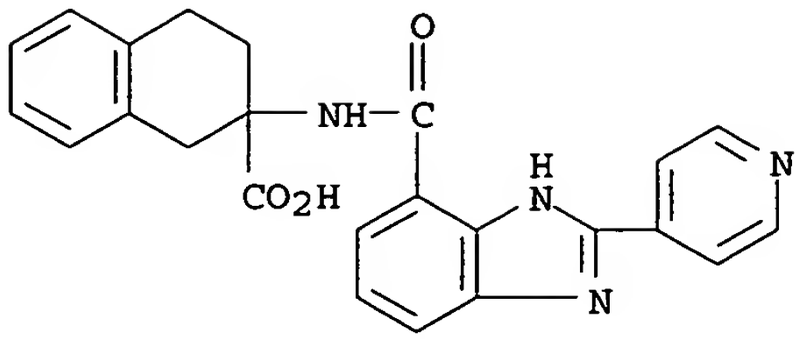


RN 313065-40-6 HCAPLUS
CN 1H-Indole-2-carboxylic acid, octahydro-1-[[2-(4-pyridinyl)-1H-benzimidazol-4-yl]carbonyl]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

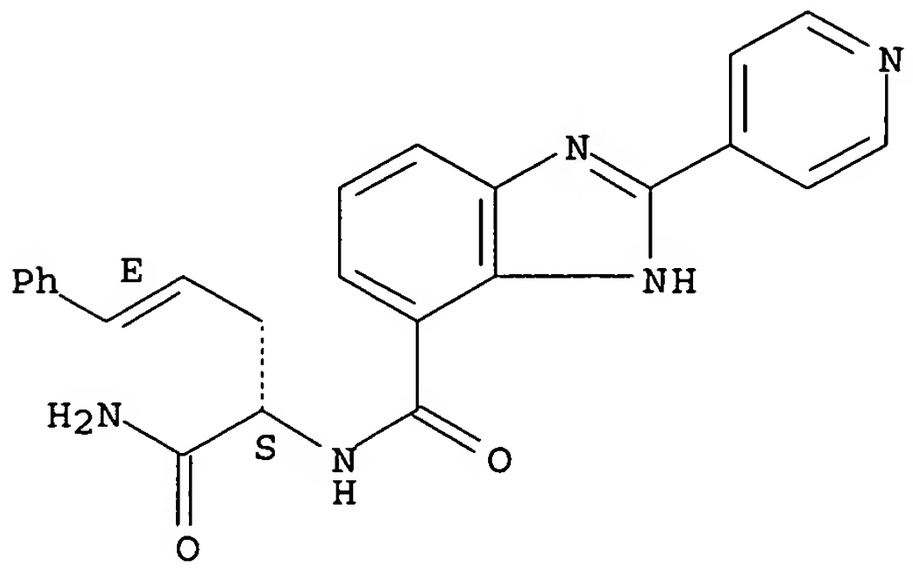


RN 313065-41-7 HCAPLUS
CN 2-Naphthalenecarboxylic acid, 1,2,3,4-tetrahydro-2-[[[2-(4-pyridinyl)-1H-benzimidazol-4-yl]carbonyl]amino]- (9CI) (CA INDEX NAME)



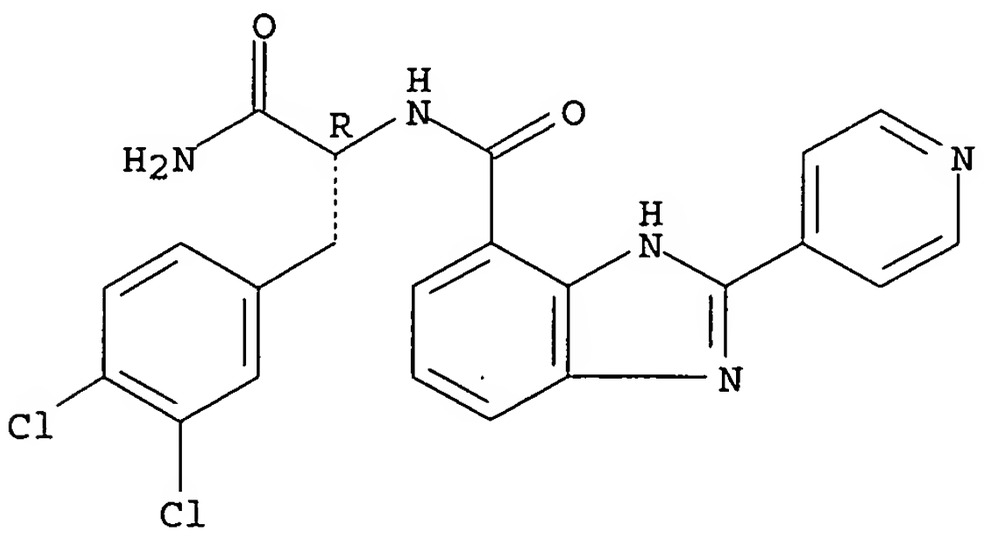
RN 313065-42-8 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S,3E)-1-(aminocarbonyl)-4-phenyl-3-butenyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



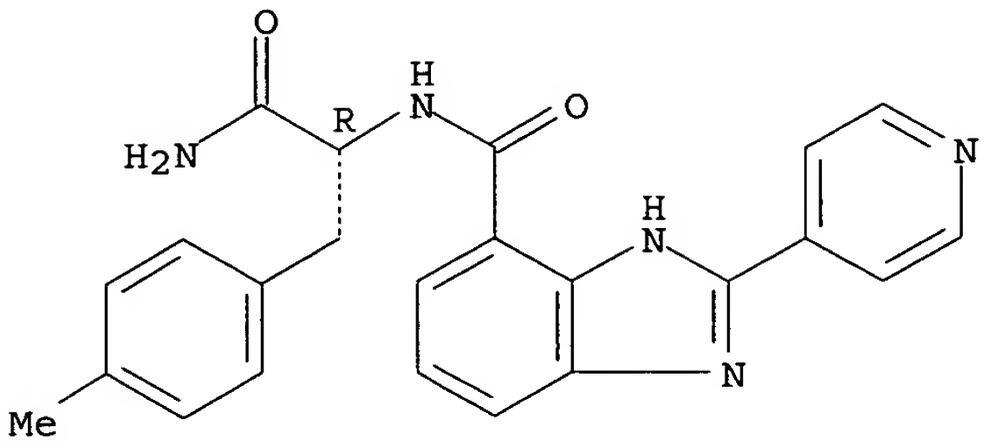
RN 313065-43-9 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1R)-2-amino-1-[(3,4-dichlorophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



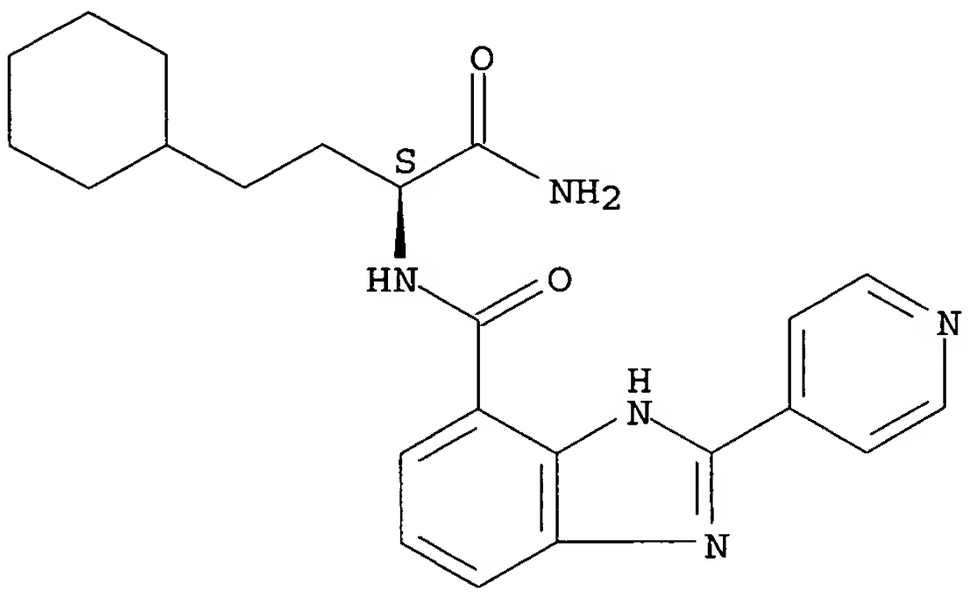
RN 313065-44-0 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1R)-2-amino-1-[(4-methylphenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



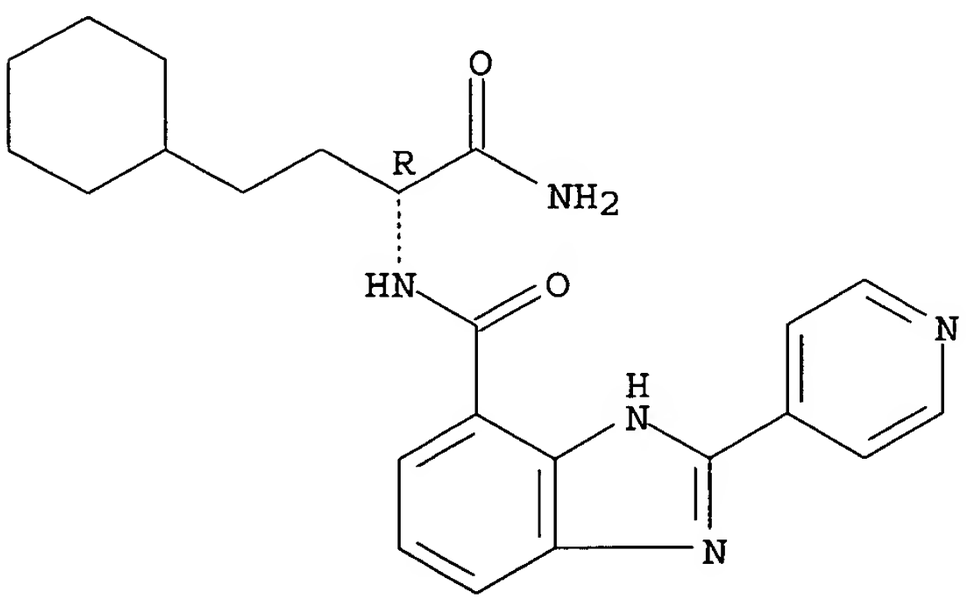
RN 313065-45-1 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-1-(aminocarbonyl)-3-cyclohexylpropyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



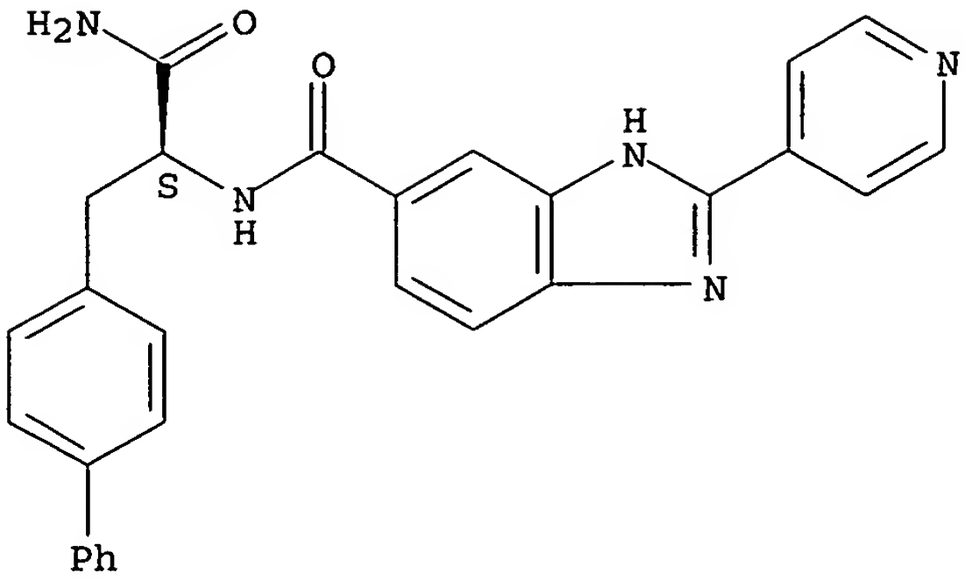
RN 313065-46-2 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1R)-1-(aminocarbonyl)-3-cyclohexylpropyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



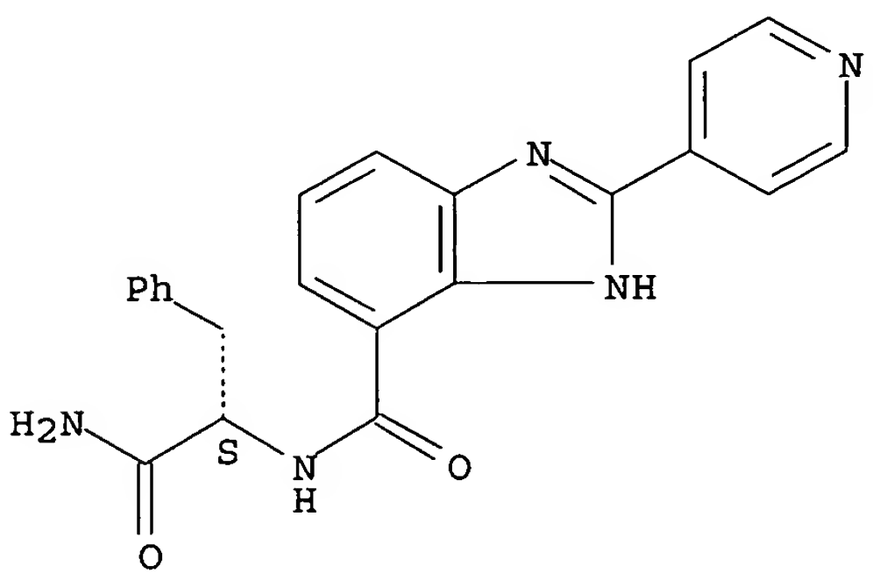
RN 313065-47-3 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-2-amino-1-([1,1'-biphenyl]-4-ylmethyl)-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



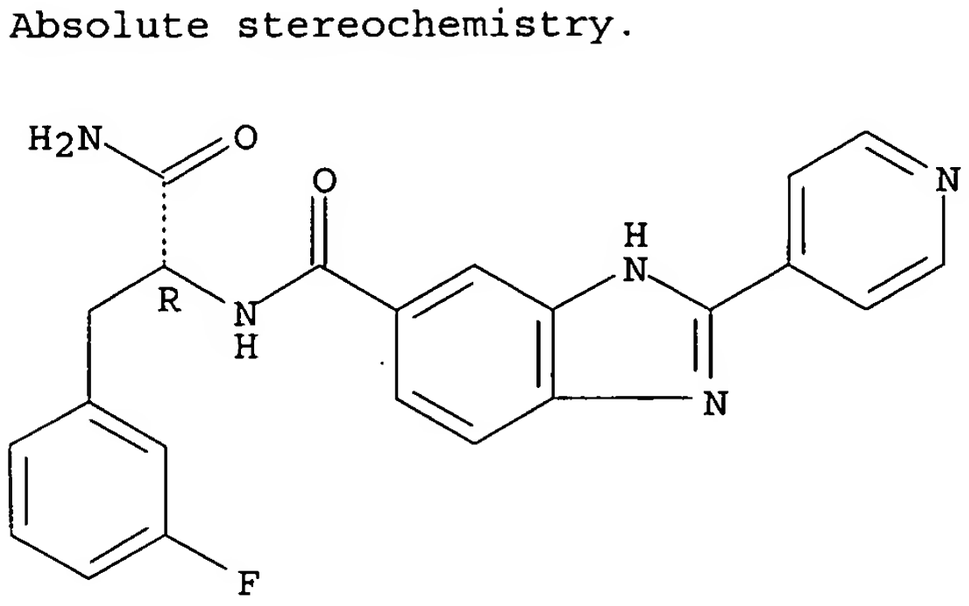
RN 313065-48-4 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-2-amino-2-oxo-1-(phenylmethyl)ethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



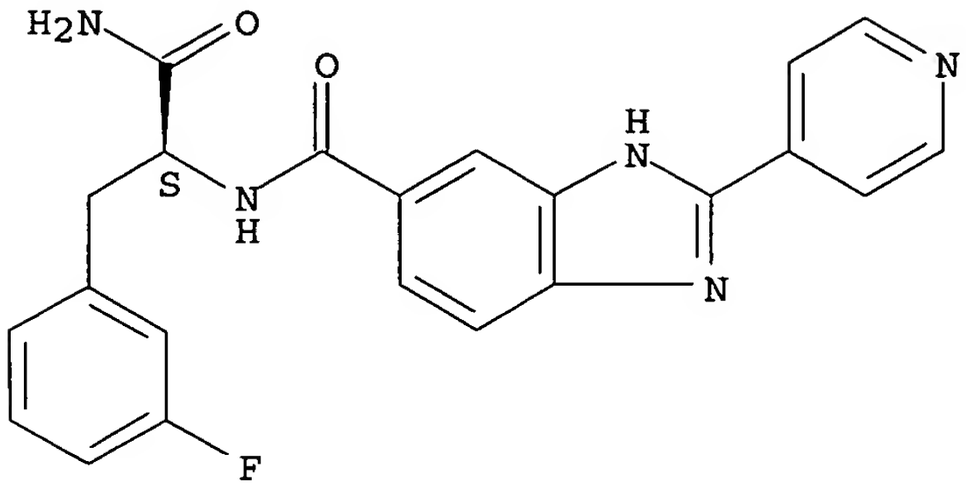
RN 313065-49-5 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1R)-2-amino-1-[(3-fluorophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



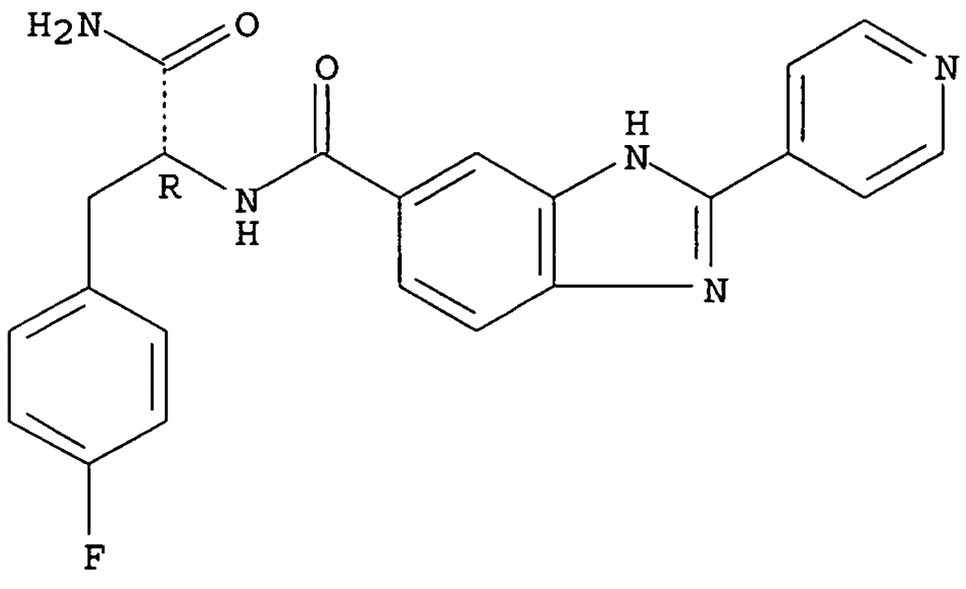
RN 313065-50-8 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-2-amino-1-[(3-fluorophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



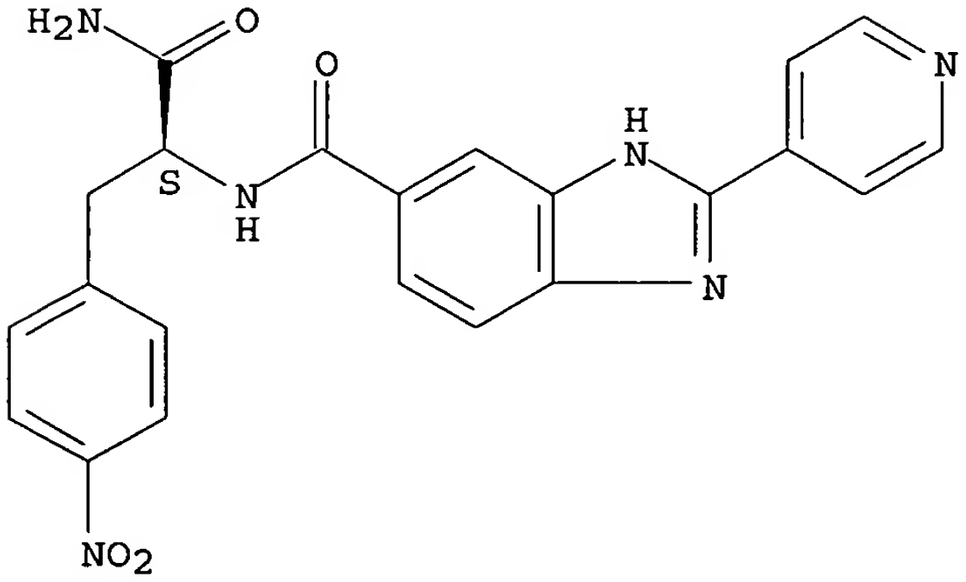
RN 313065-51-9 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1R)-2-amino-1-[(4-fluorophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

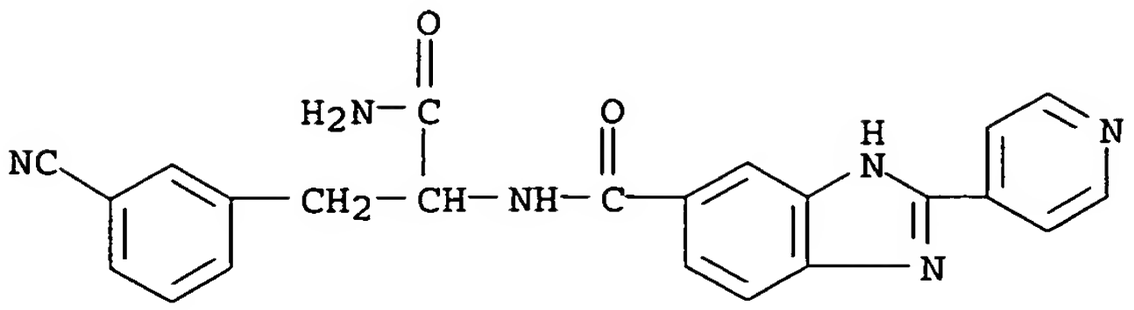


RN 313065-52-0 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-2-amino-1-[(4-nitrophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

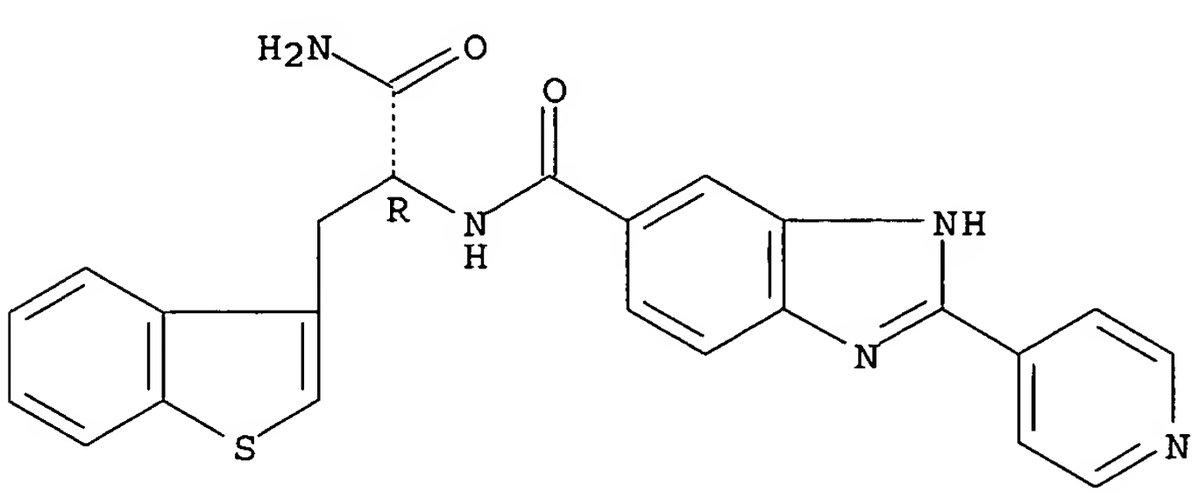


RN 313065-53-1 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[2-amino-1-[(3-cyanophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

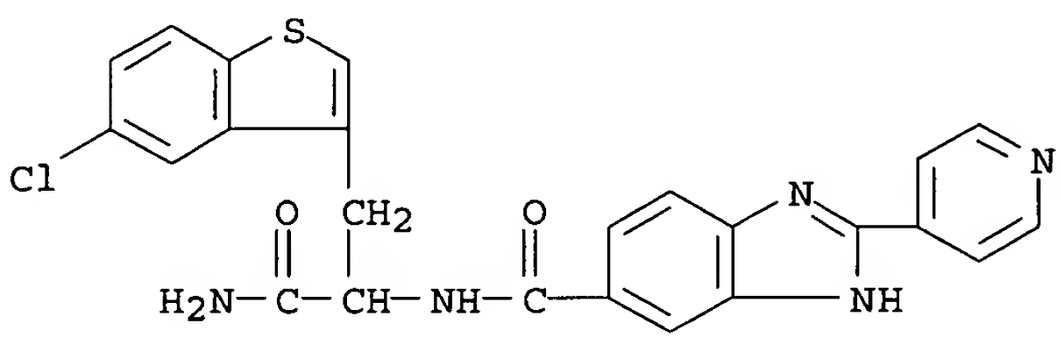


RN 313065-54-2 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1R)-2-amino-1-(benzo[b]thien-3-ylmethyl)-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

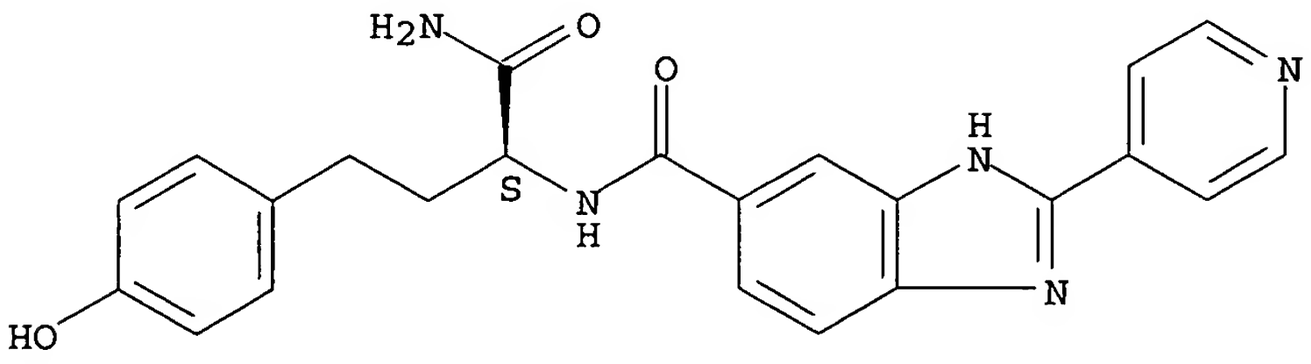


RN 313065-55-3 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[2-amino-1-[(5-chlorobenzo[b]thien-3-yl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)



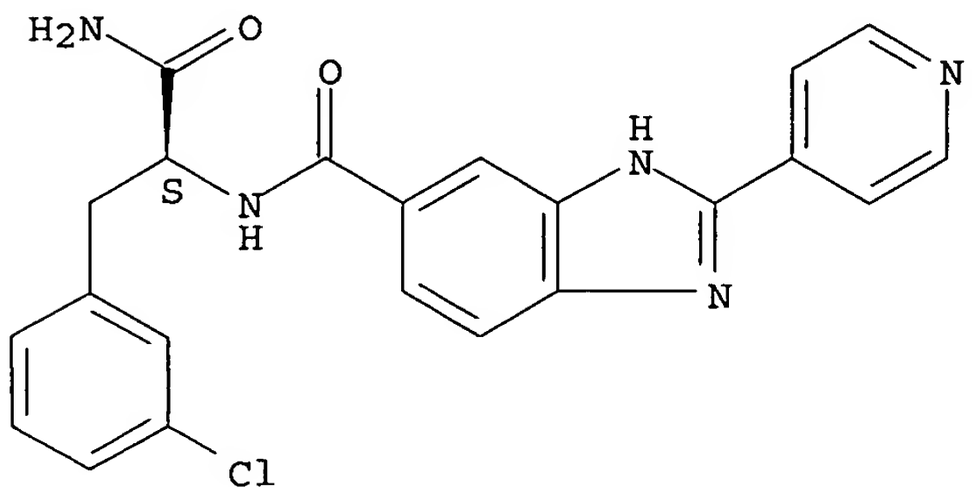
RN 313065-56-4 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-1-(aminocarbonyl)-3-(4-hydroxyphenyl)propyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



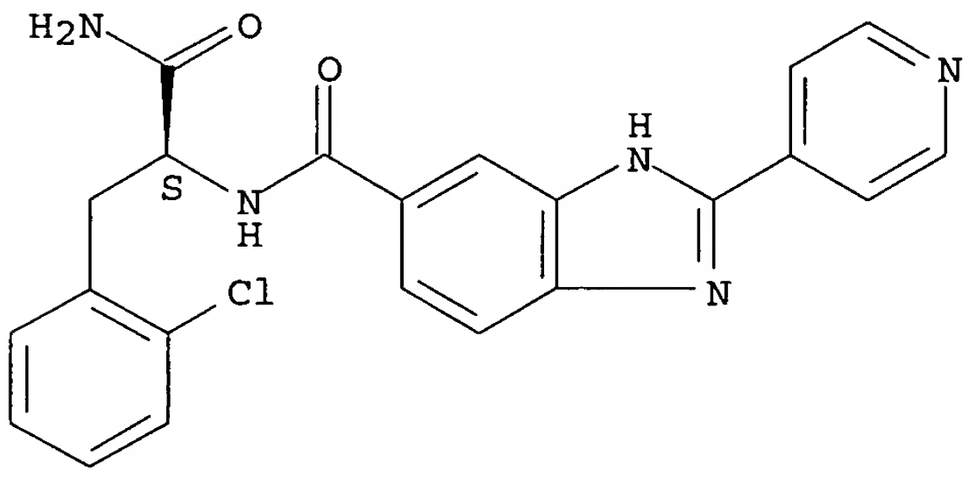
RN 313065-57-5 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-2-amino-1-[(3-chlorophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



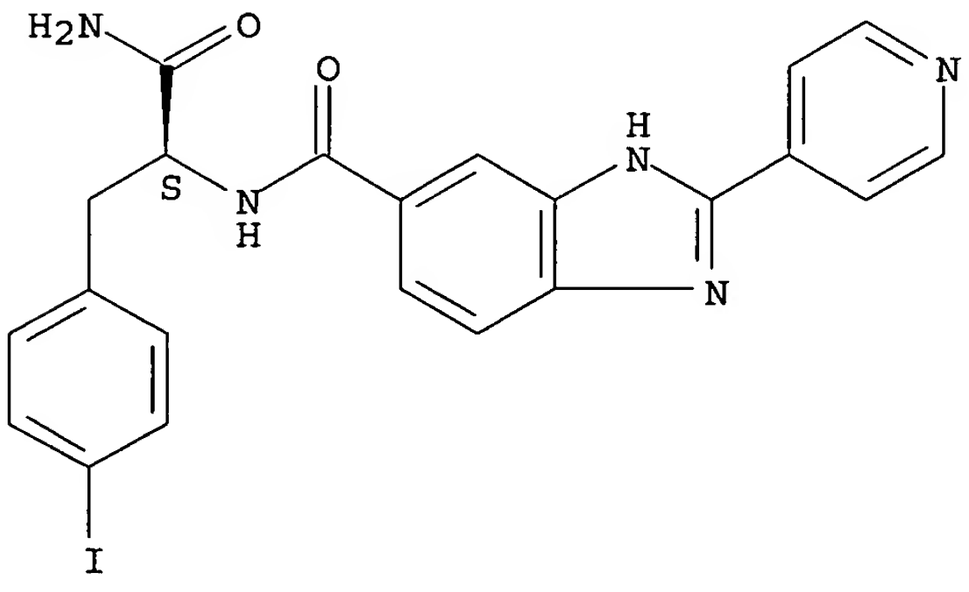
RN 313065-58-6 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-2-amino-1-[(2-chlorophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



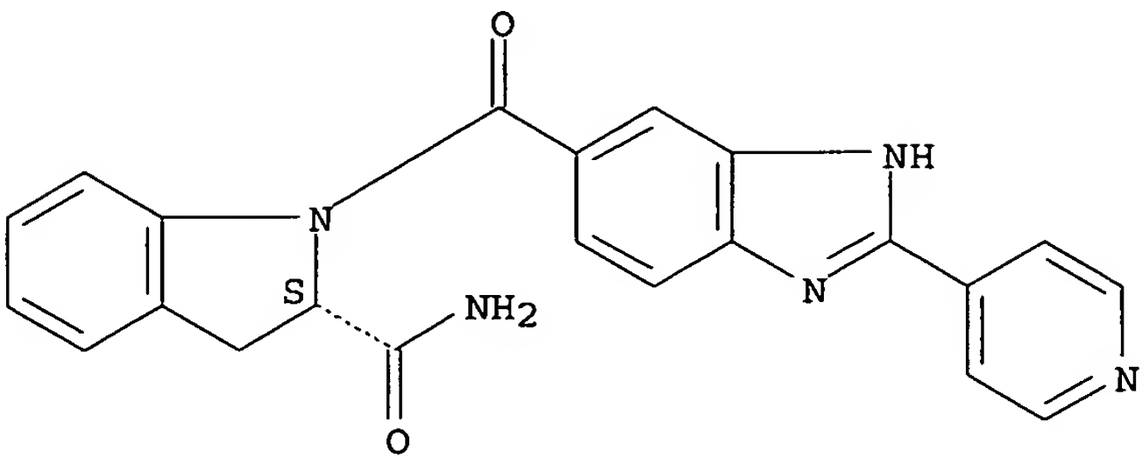
RN 313065-59-7 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-2-amino-1-[(4-iodophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

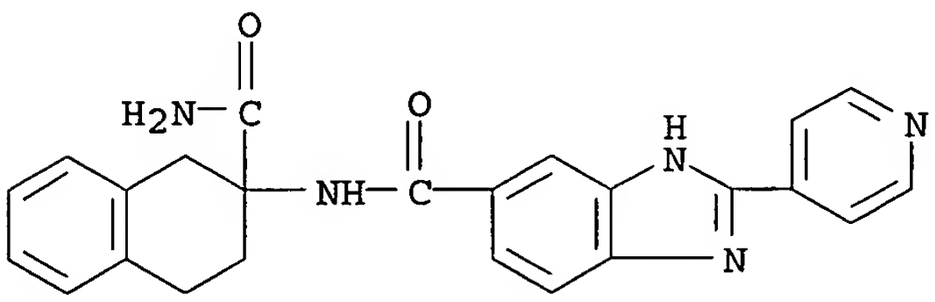


RN 313065-60-0 HCAPLUS
CN 1H-Indole-2-carboxamide, 2,3-dihydro-1-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

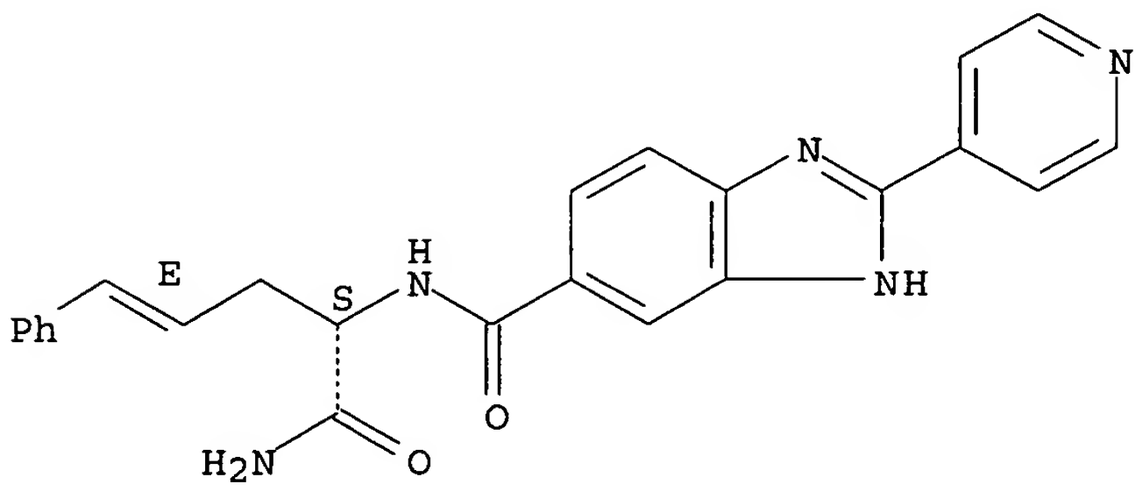


RN 313065-61-1 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[2-(aminocarbonyl)-1,2,3,4-tetrahydro-2-naphthalenyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)



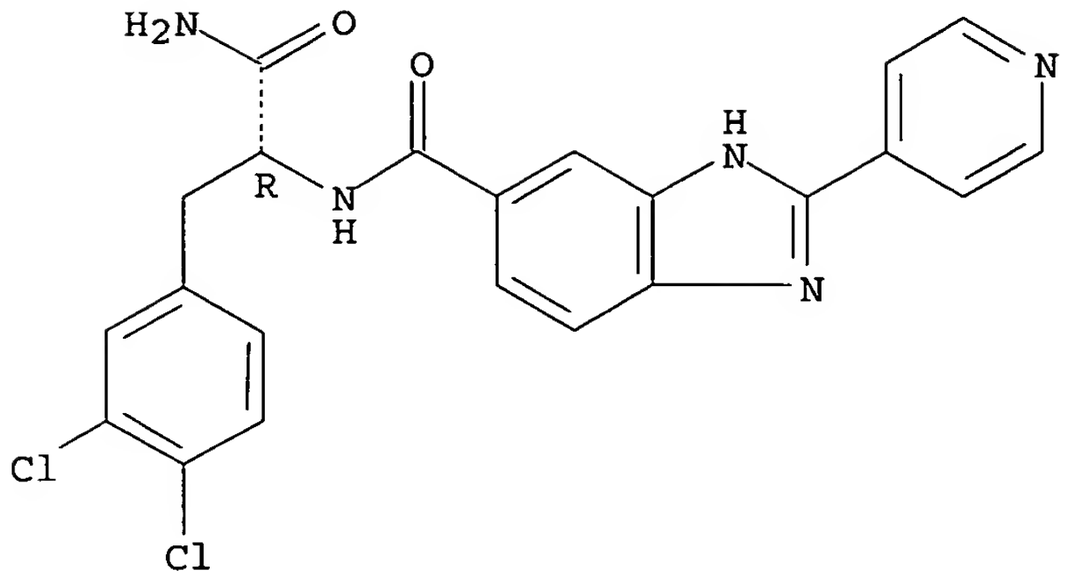
RN 313065-62-2 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S,3E)-1-(aminocarbonyl)-4-phenyl-3-butenyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



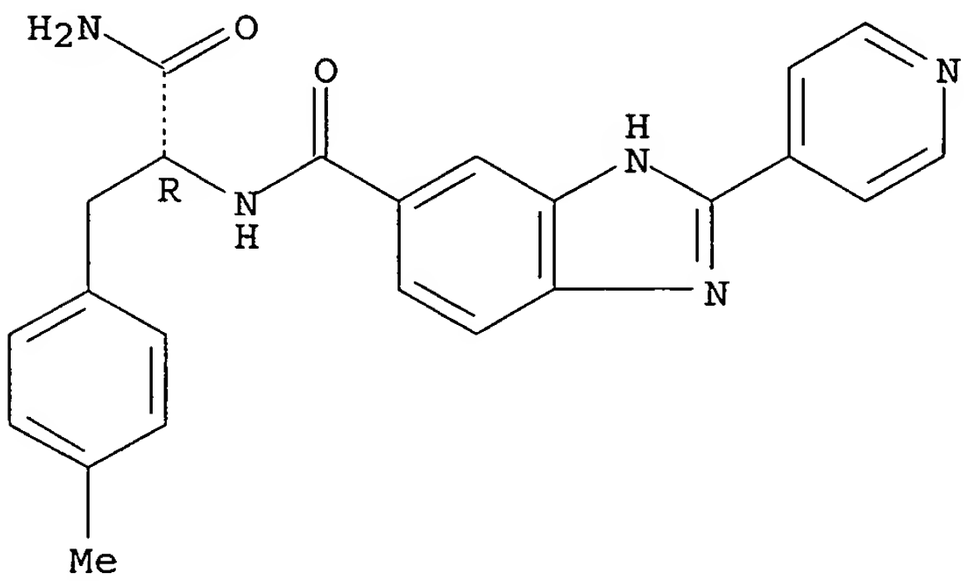
RN 313065-63-3 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1R)-2-amino-1-[(3,4-dichlorophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



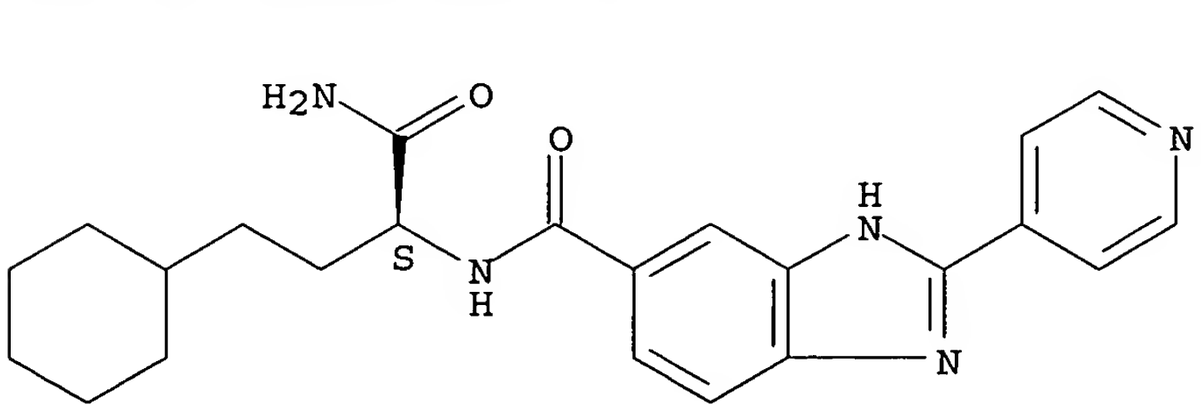
RN 313065-64-4 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1R)-2-amino-1-[(4-methylphenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



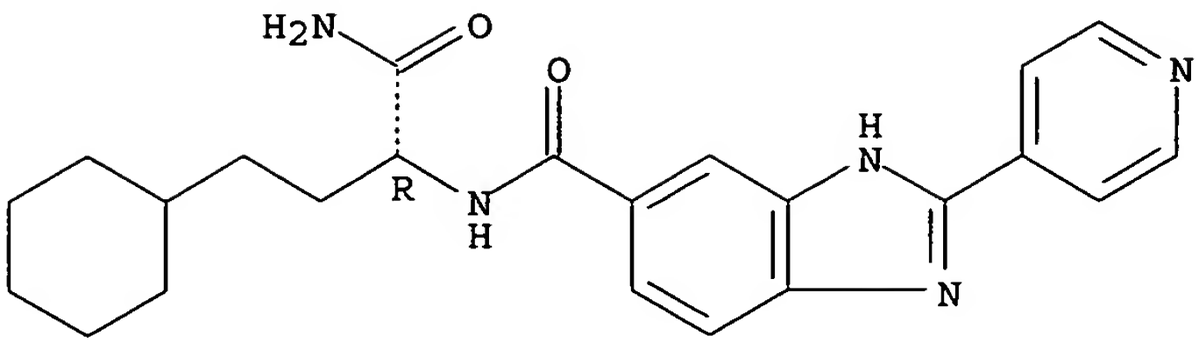
RN 313065-65-5 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-1-(aminocarbonyl)-3-cyclohexylpropyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



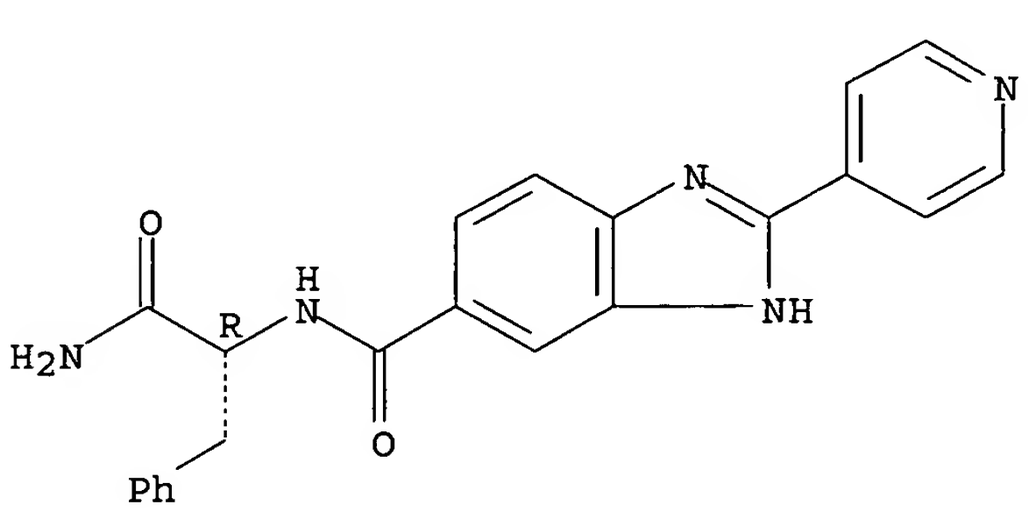
RN 313065-66-6 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1R)-1-(aminocarbonyl)-3-cyclohexylpropyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



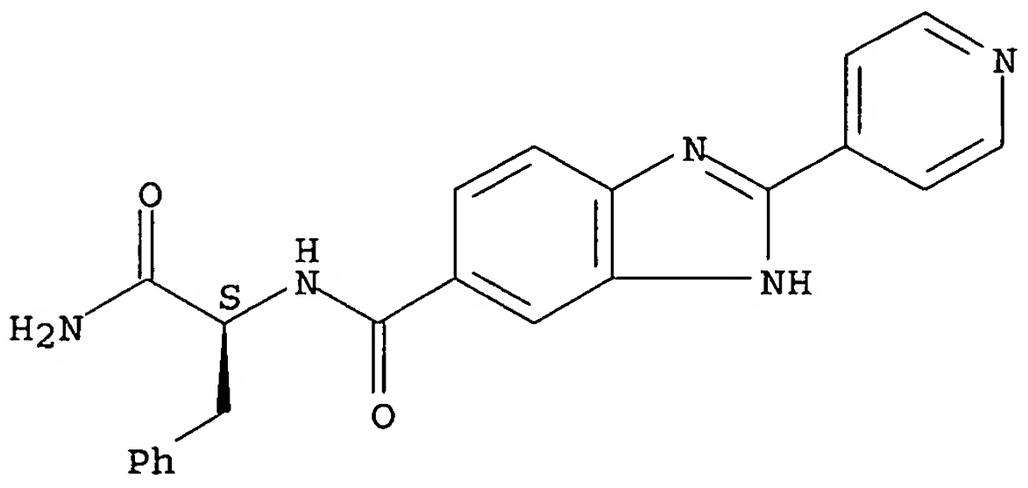
RN 313065-67-7 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1R)-2-amino-2-oxo-1-(phenylmethyl)ethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



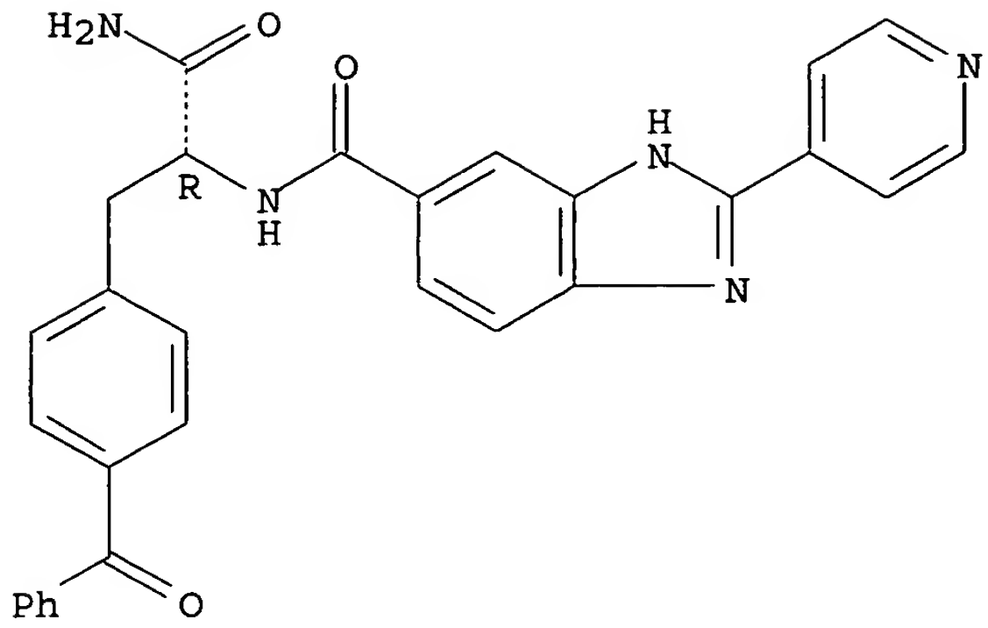
RN 313065-68-8 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-2-amino-2-oxo-1-(phenylmethyl)ethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



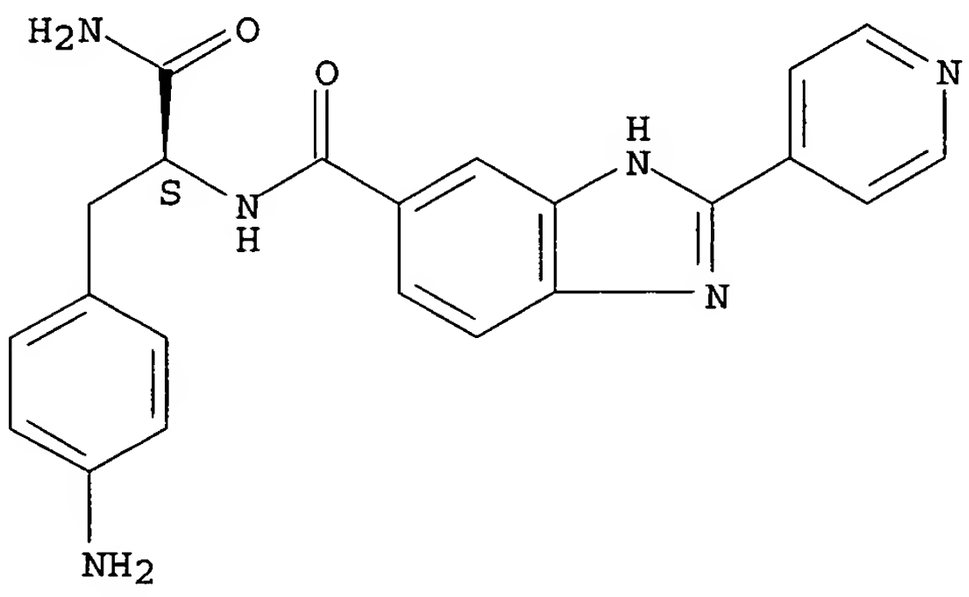
RN 313065-69-9 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1R)-2-amino-1-[(4-benzoylphenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



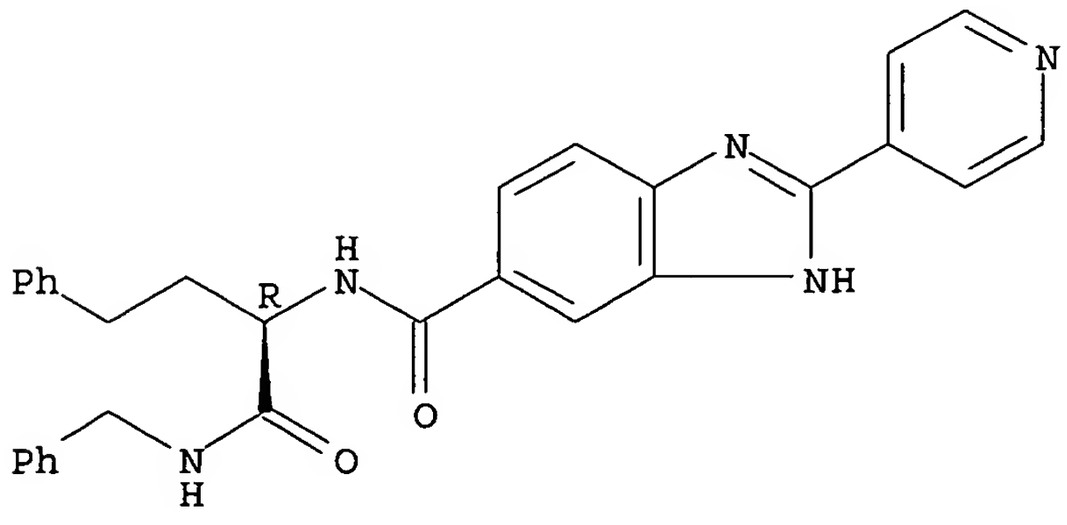
RN 313065-71-3 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-2-amino-1-[(4-aminophenyl)methyl]-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 313065-72-4 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1R)-3-phenyl-1-[[(phenylmethyl)amino]carbonyl]propyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

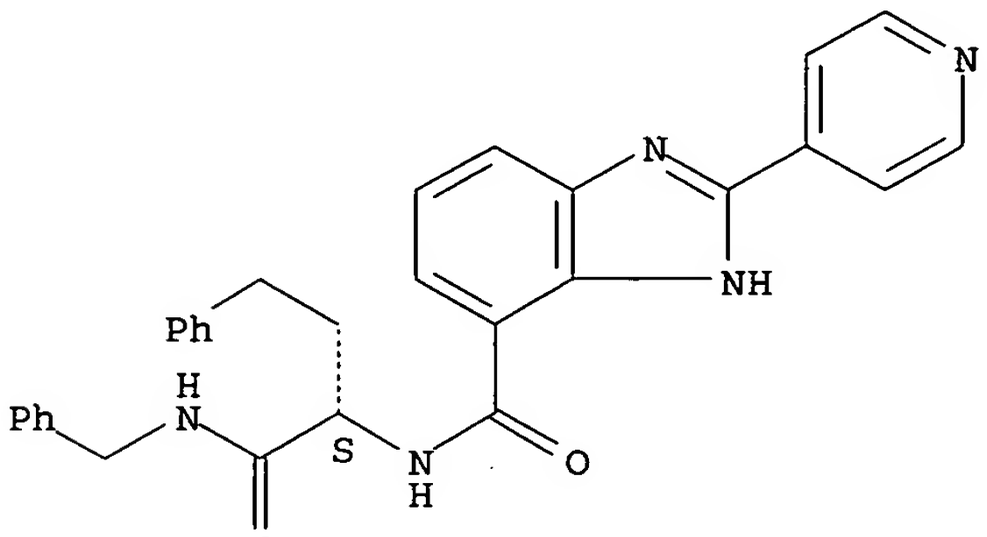
Absolute stereochemistry.



RN 313065-73-5 HCAPLUS

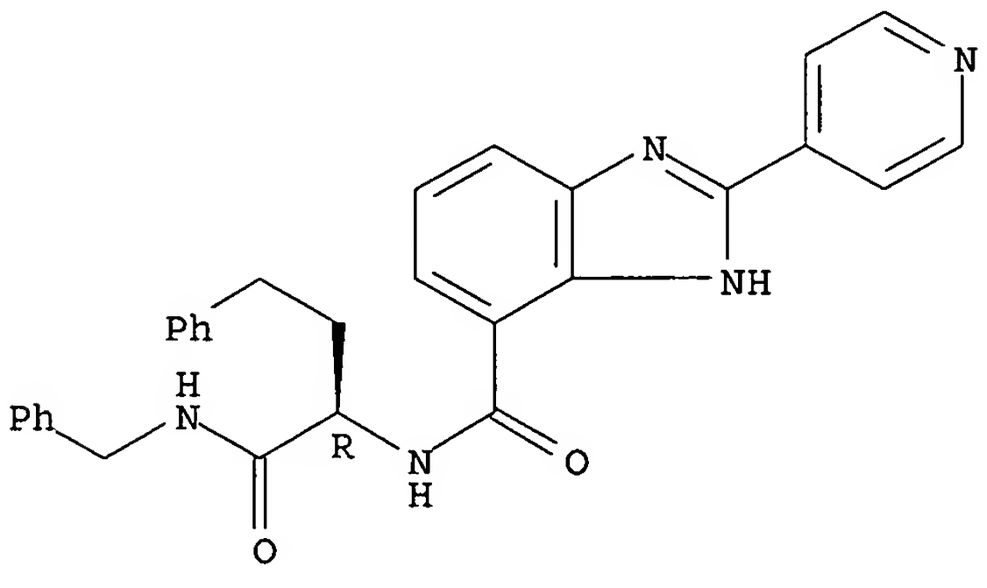
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-3-phenyl-1-[[(phenylmethyl)amino]carbonyl]propyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



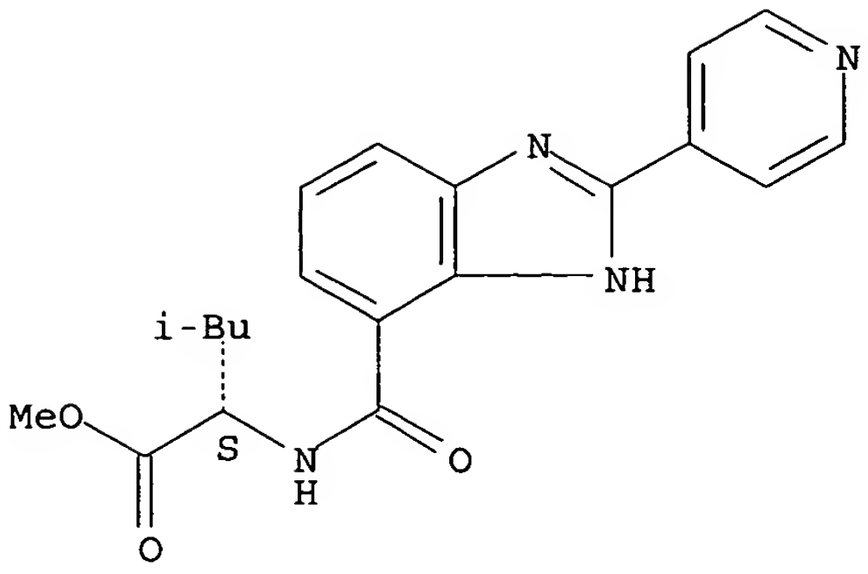
RN 313065-74-6 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1R)-3-phenyl-1-[[(phenylmethyl)amino]carbonyl]propyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



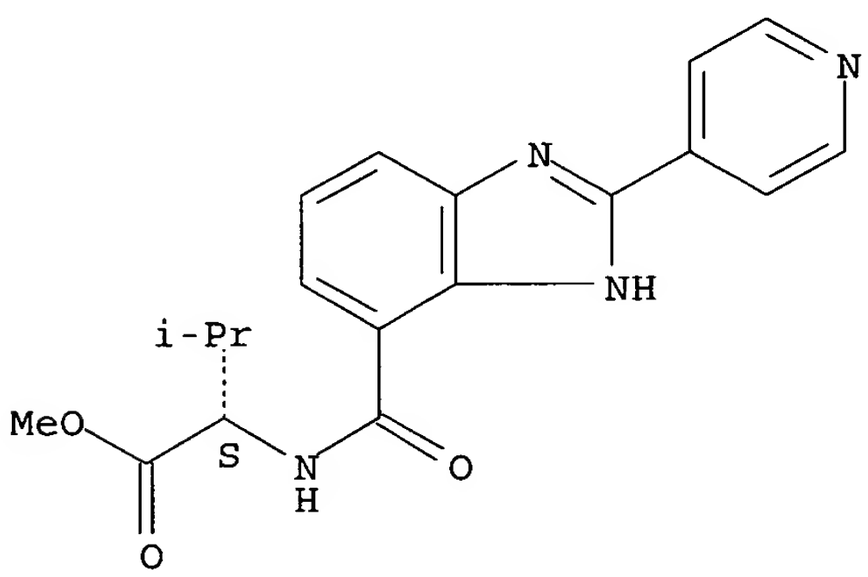
RN 313065-81-5 HCAPLUS
CN L-Leucine, N-[[2-(4-pyridinyl)-1H-benzimidazol-4-yl]carbonyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



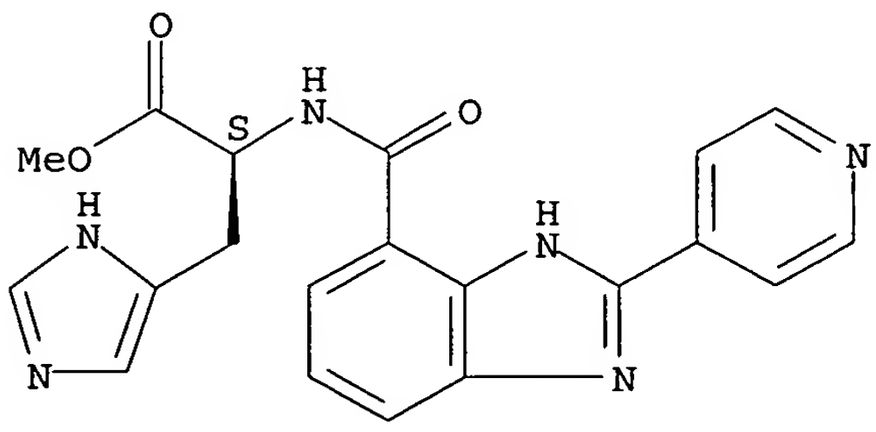
RN 313065-84-8 HCAPLUS
CN L-Valine, N-[[2-(4-pyridinyl)-1H-benzimidazol-4-yl]carbonyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



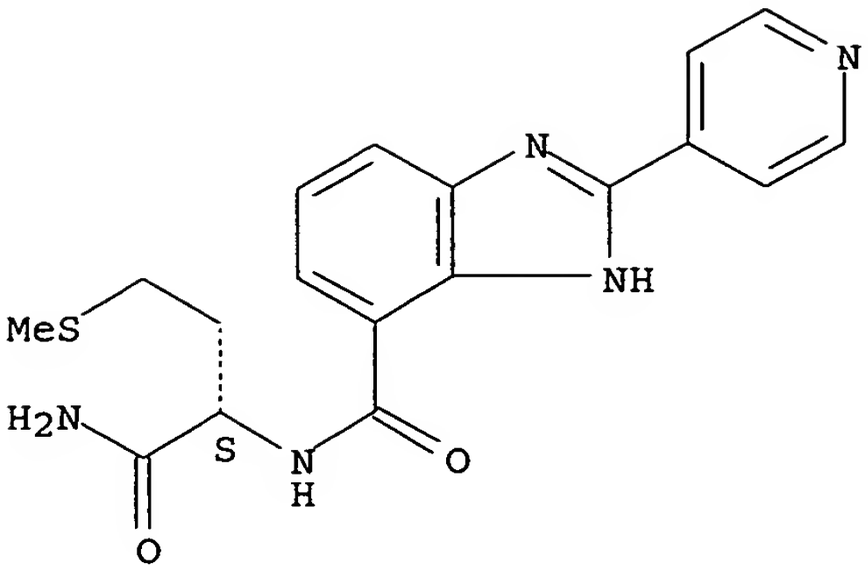
RN 313065-88-2 HCAPLUS
CN L-Histidine, N-[[2-(4-pyridinyl)-1H-benzimidazol-4-yl]carbonyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



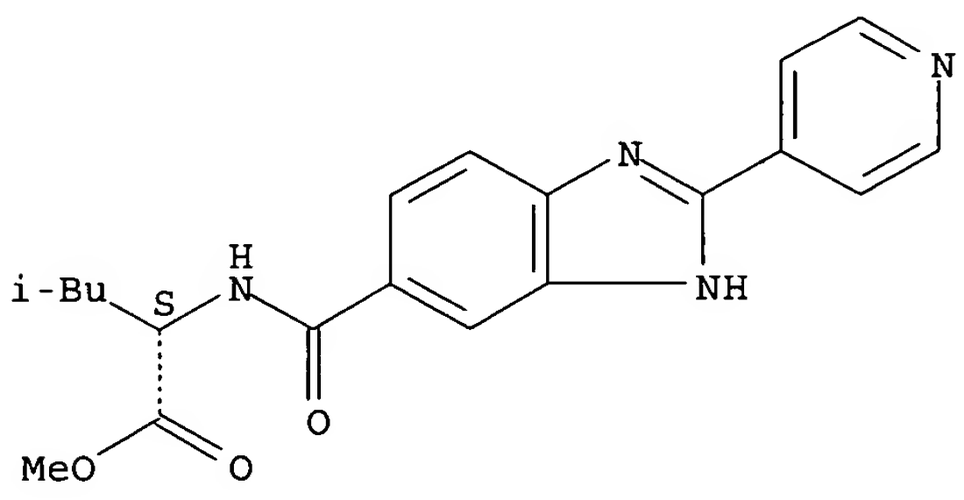
RN 313065-90-6 HCAPLUS
CN 1H-Benzimidazole-4-carboxamide, N-[(1S)-1-(aminocarbonyl)-3-(methylthio)propyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



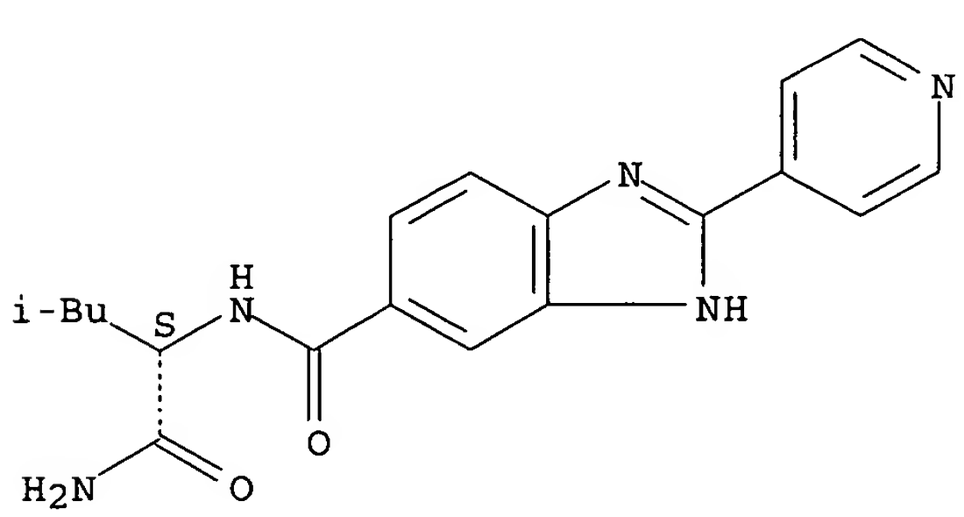
RN 313065-92-8 HCAPLUS
CN L-Leucine, N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



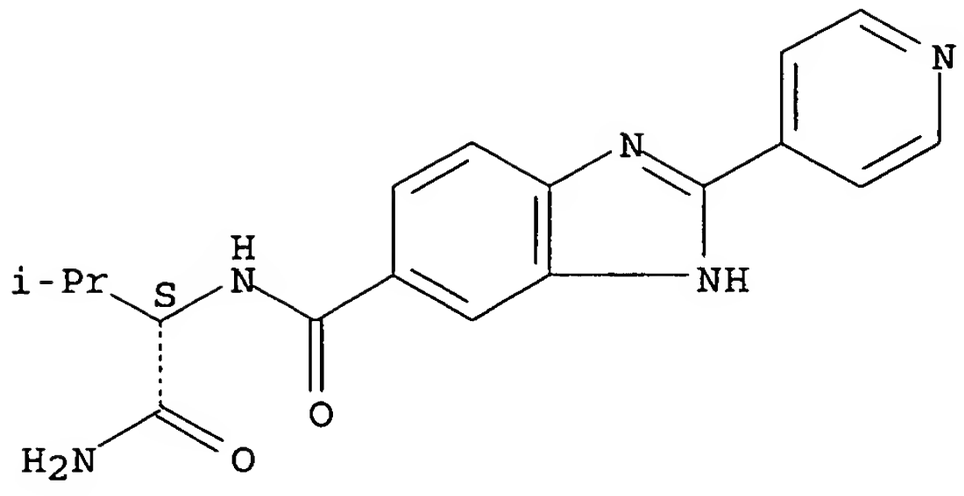
RN 313065-93-9 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-1-(aminocarbonyl)-3-methylbutyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

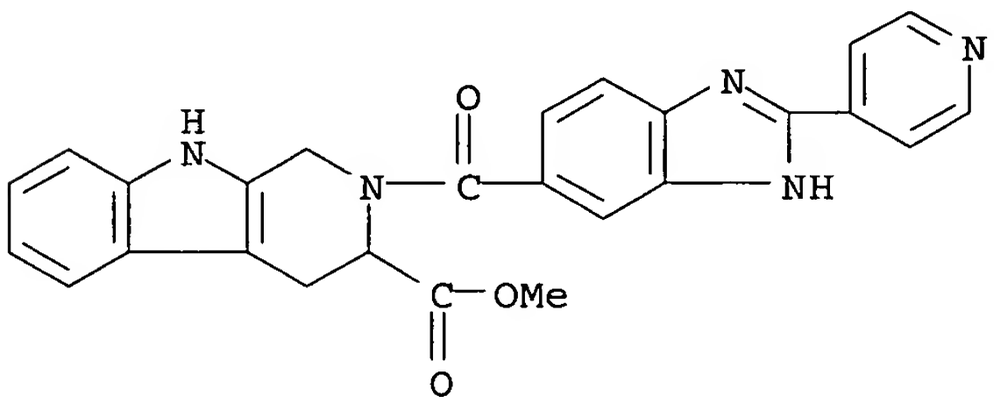


RN 313065-94-0 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

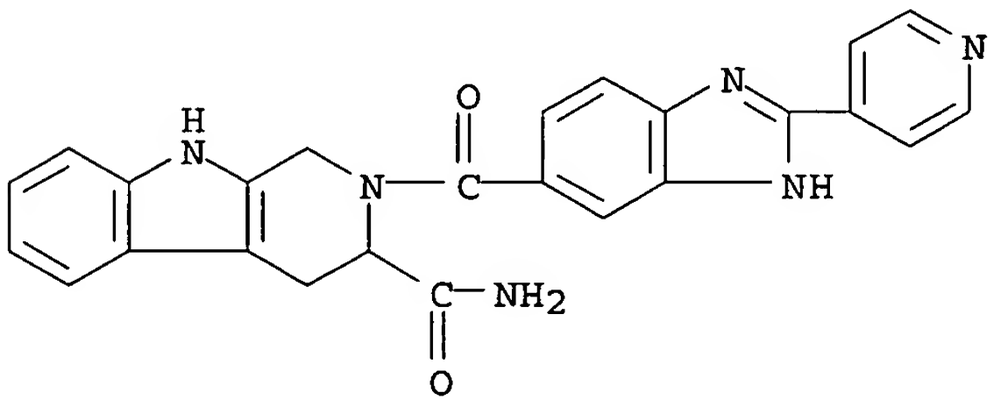
Absolute stereochemistry.



RN 313065-95-1 HCAPLUS
CN 1H-Pyrido[3,4-b]indole-3-carboxylic acid, 2,3,4,9-tetrahydro-2-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]-, methyl ester (9CI) (CA INDEX NAME)

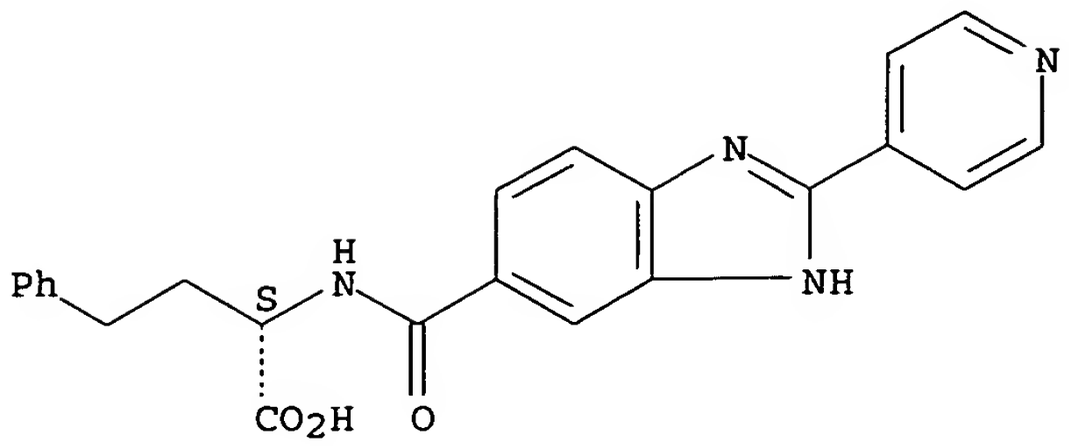


RN 313065-96-2 HCAPLUS
CN 1H-Pyrido[3,4-b]indole-3-carboxamide, 2,3,4,9-tetrahydro-2-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]- (9CI) (CA INDEX NAME)



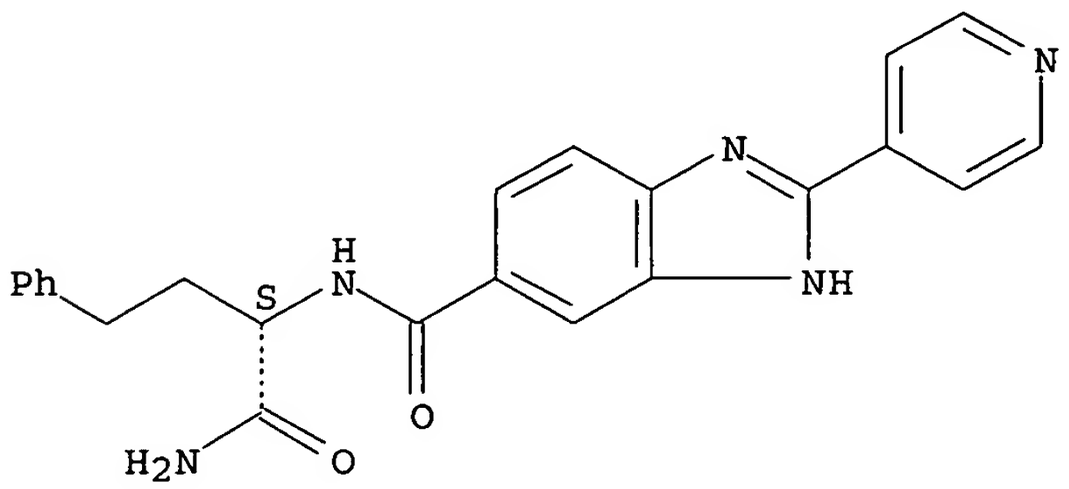
RN 313065-98-4 HCAPLUS
CN Benzenebutanoic acid, α-[[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]amino]-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



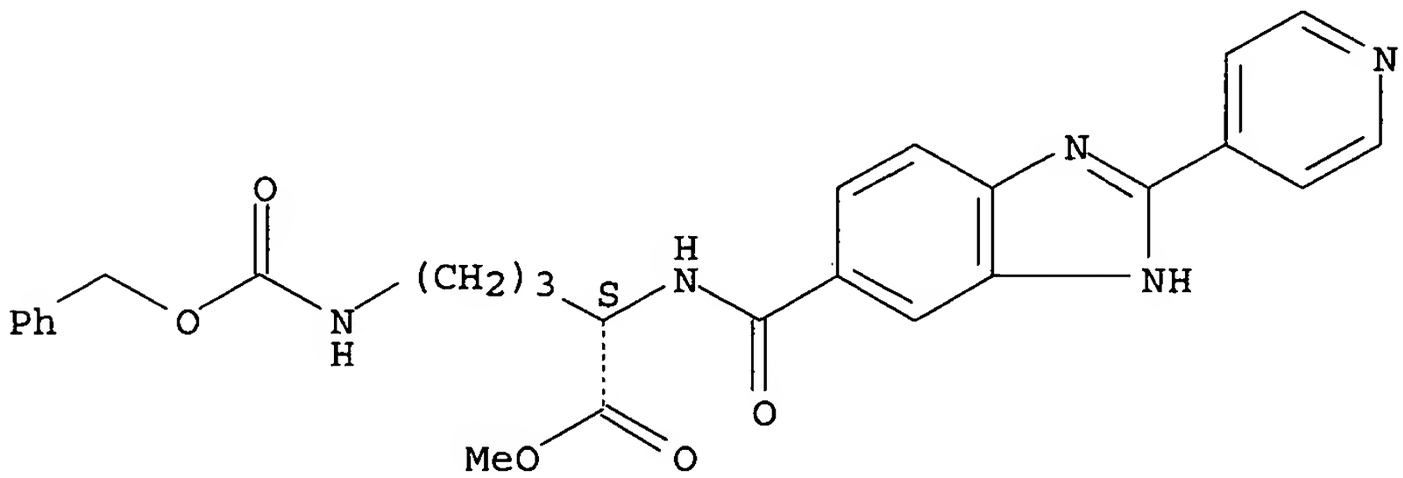
RN 313065-99-5 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-1-(aminocarbonyl)-3-phenylpropyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



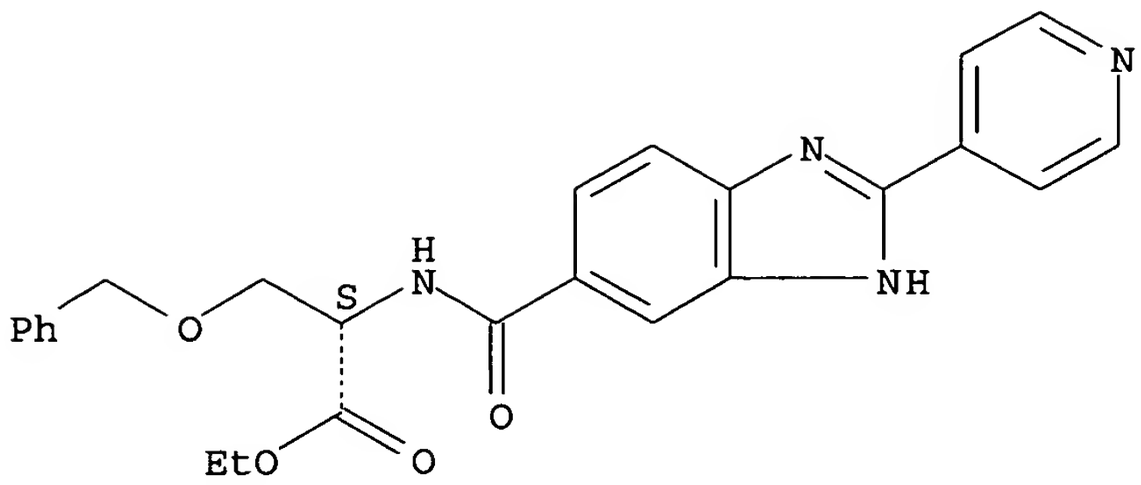
RN 313066-00-1 HCAPLUS
CN L-Ornithine, N5-[(phenylmethoxy)carbonyl]-N2-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



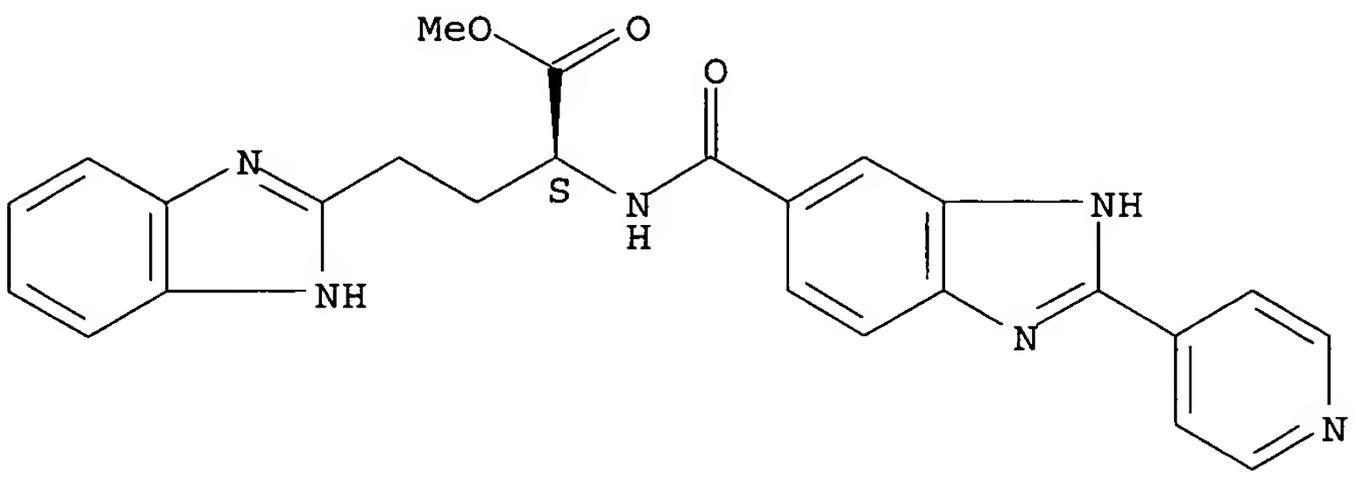
RN 313066-01-2 HCAPLUS
CN L-Serine, O-(phenylmethyl)-N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



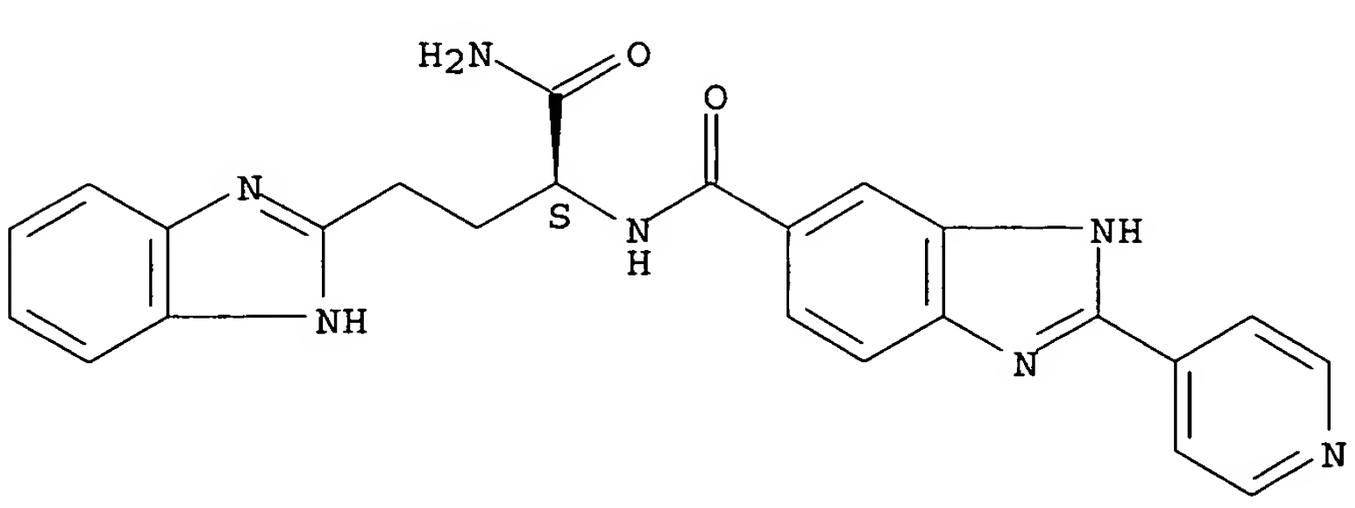
RN 313066-02-3 HCAPLUS
CN 1H-Benzimidazole-2-butanoic acid, α-[[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]amino]-, methyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



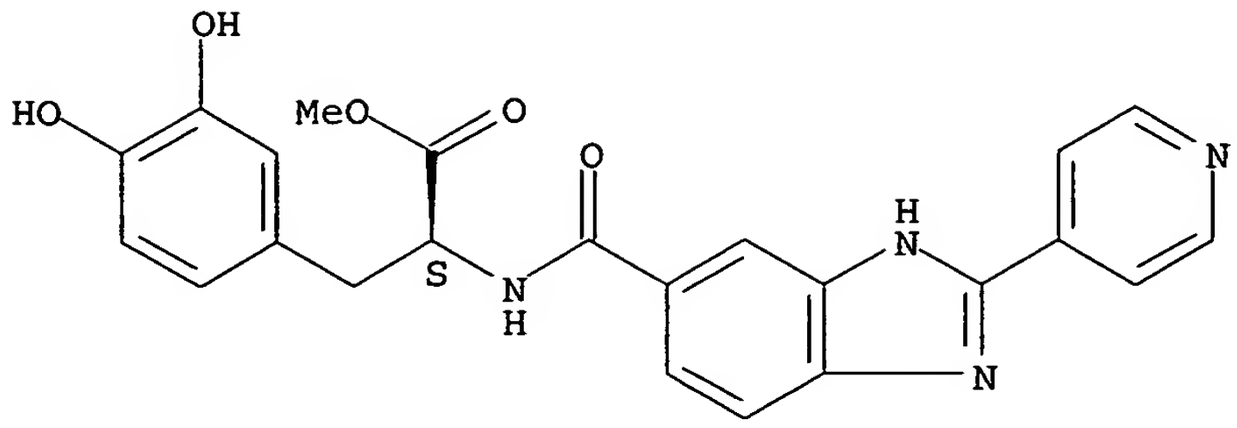
RN 313066-03-4 HCAPLUS
CN 1H-Benzimidazole-2-butanamide, α-[[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]amino]-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



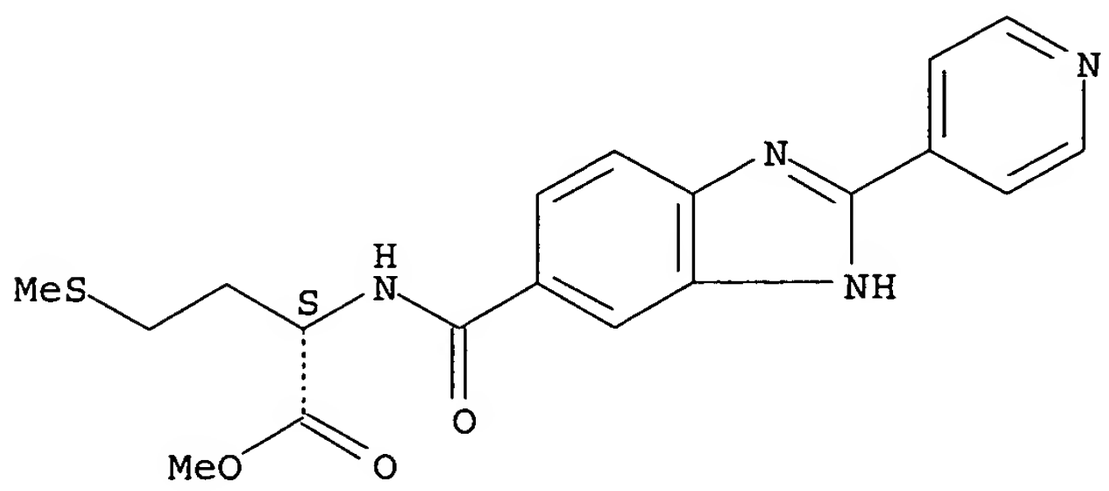
RN 313066-05-6 HCAPLUS
CN L-Tyrosine, 3-hydroxy-N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



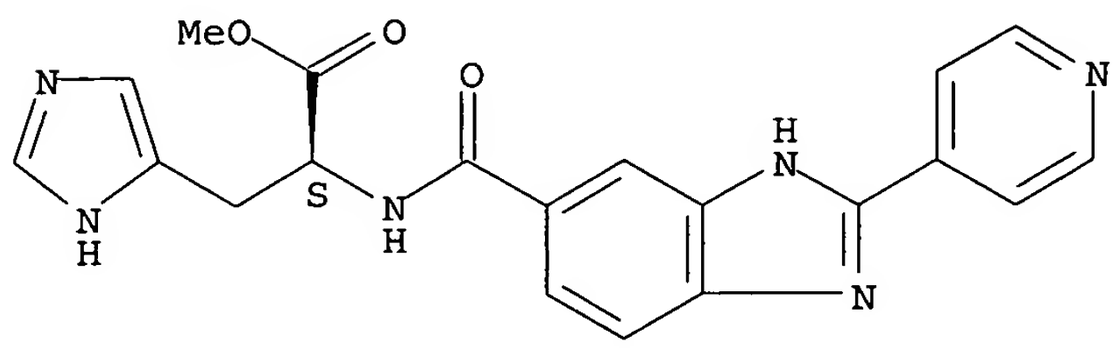
RN 313066-09-0 HCAPLUS
CN L-Methionine, N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



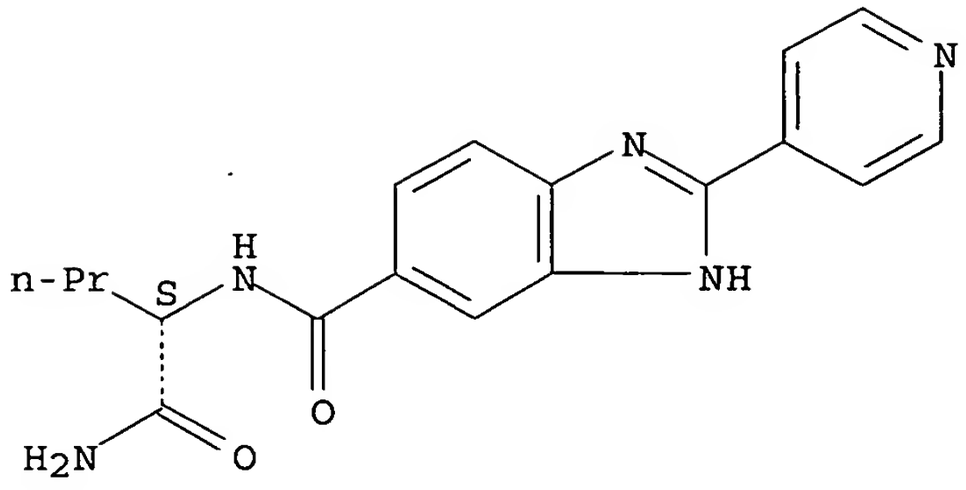
RN 313066-10-3 HCAPLUS
CN L-Histidine, N-[[2-(4-pyridinyl)-1H-benzimidazol-5-yl]carbonyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

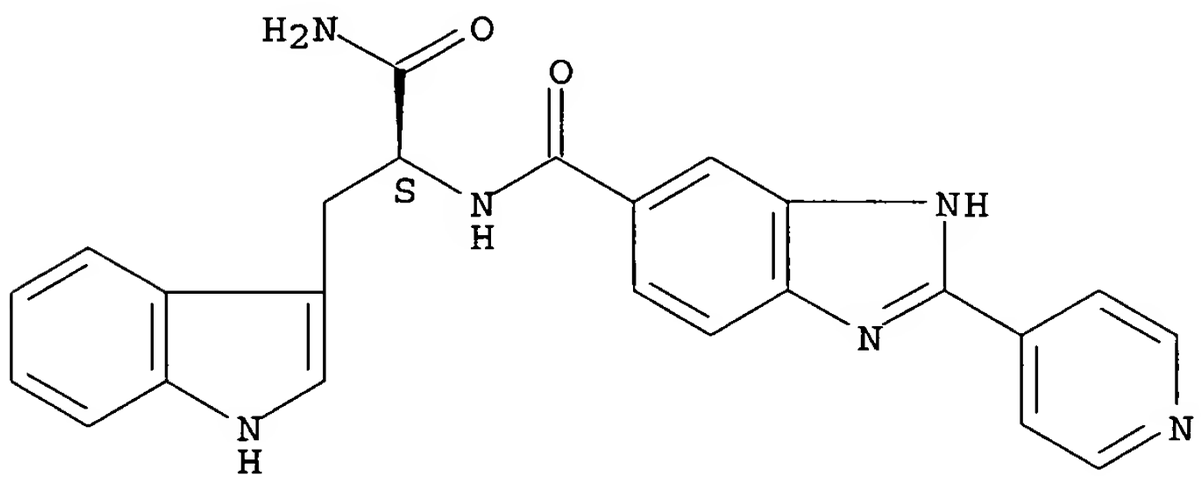


RN 313066-11-4 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-1-(aminocarbonyl)butyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 313066-12-5 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, N-[(1S)-2-amino-1-(1H-indol-3-ylmethyl)-2-oxoethyl]-2-(4-pyridinyl)- (9CI) (CA INDEX NAME)
Absolute stereochemistry.



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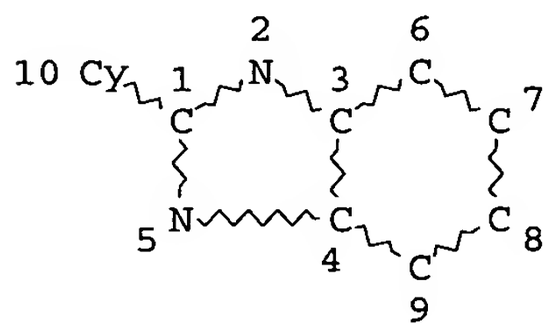
L1 STR



NODE ATTRIBUTES:
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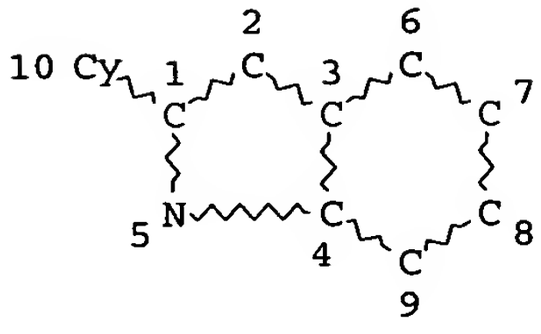
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC 1
NUMBER OF NODES IS 10

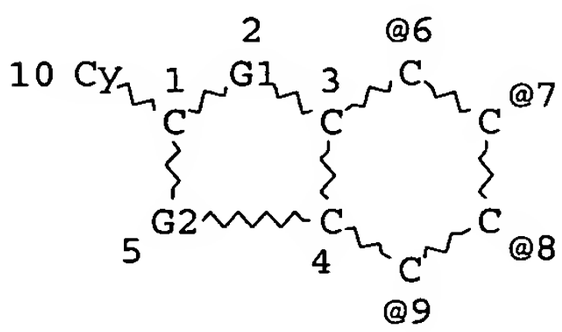
STEREO ATTRIBUTES: NONE
L2 STR

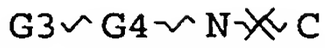


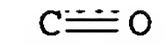
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

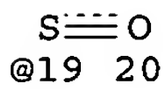
GRAPH ATTRIBUTES:
RSPEC 1
NUMBER OF NODES IS 10

STEREO ATTRIBUTES: NONE
L3 100862 SEA FILE=REGISTRY SSS FUL L1 OR L2
L4 STR









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VAR G3=6/7/8/9
VAR G4=17/19
NODE ATTRIBUTES:
NSPEC IS RC AT 13
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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 20

STEREO ATTRIBUTES: NONE
L5 3405 SEA FILE=REGISTRY SUB=L3 SSS FUL L4
L6 206 SEA FILE=HCAPLUS ABB=ON PLU=ON L5
L7 6 SEA FILE=HCAPLUS ABB=ON PLU=ON L6 AND (PAIN OR HEADACHE OR MIGRAINE OR CEPHALA? OR ?HERPES? OR ?ZOSTER? OR ?NEURALG?)
L13 7274 SEA FILE=HCAPLUS ABB=ON PLU=ON ?KAPPA?(L)KINASE
L14 5 SEA FILE=HCAPLUS ABB=ON PLU=ON L13 AND L6
L15 3 SEA FILE=HCAPLUS ABB=ON PLU=ON L14 NOT L7
L21 102269 SEA FILE=HCAPLUS ABB=ON PLU=ON PAIN+ALL/CV
L22 6 SEA FILE=HCAPLUS ABB=ON PLU=ON L6 AND L21
L23 1 SEA FILE=HCAPLUS ABB=ON PLU=ON L22 NOT L7

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L24             4 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L15 OR L23
L26            16 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ("RITZELER O"/AU OR "RITZELER
                  OLAF"/AU)
L27            11 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L26 NOT (L7 OR L24)


=> d ibib abs l27 1-11

L27  ANSWER 1 OF 11  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2004:1121975  HCAPLUS
DOCUMENT NUMBER:          142:175255
TITLE:                    Protein Kinase C Pathway Is Involved in
                          Transcriptional Regulation of C-Reactive Protein
                          Synthesis in Human Hepatocytes
AUTHOR(S):                Ivashchenko, Yuri; Kramer, Frank; Schaefer, Stefan;
                          Bucher, Andrea; Veit, Kerstin; Hombach, Vinzenz;
                          Busch, Andreas; Ritzeler, Olaf; Dedio,
                          Juergen; Torzewski, Jan
CORPORATE SOURCE:         Aventis Pharma Deutschland GmbH, Frankfurt am Main,
                          Germany
SOURCE:                   Arteriosclerosis, Thrombosis, and Vascular Biology
                          (2005), 25(1), 186-192
                          CODEN: ATVBFA; ISSN: 1079-5642
PUBLISHER:                Lippincott Williams & Wilkins
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   Objective- C-Reactive protein (CRP) is the prototype acute phase protein
     and a cardiovascular risk factor.  Interleukin-1β (IL-1β) and
     IL-6 stimulate CRP synthesis in hepatocytes.  The authors searched for
     addnl. pathways regulating CRP expression.  Methods and Results- Primary
     human hepatocytes (PHHs) were treated with IL-1β, IL-6, and protein
     kinase C (PKC) activator phorbol 12,13-dibutyrate (PDBu).  CRP was
     analyzed by quant. RT-PCR and ELISA.  PDBu significantly induced CRP
     transcription by 21.0-fold and protein release by 2.9-fold.
     Transcriptional regulation was studied in detail in hepatoma G2 (HepG2)
     cells stably transfected with the 1-kb CRP promoter (HepG2-ABEK14 cells).
     In these cells, PDBu significantly induced CRP transcription by 5.39-fold.
     Competetive inhibition with bisindolylmaleimide derivative LY333531 abolished
     PDBu-mediated promoter activation.  Competetive inhibition with IκB
     kinase inhibitor I229 also inhibited PDBu effects.  Importantly, IL-8
     significantly induced CRP release in PHHs by 58.675-fold, which was
     blockable by LY333531.  Conclusions- This study describes a novel
     PKC-dependent transcriptional regulation of CRP gene expression, which, in
     analogy to the classical IL-1β and IL-6 pathways, is operational in
     hepatocytes only.  It also identifies IL-8 as a potential physiol. PKC
     activator.  HepG2-ABEK14 cells may be useful for high throughput screening
     to identify inhibitors of CRP synthesis for the prevention of
     cardiovascular disease.
REFERENCE COUNT:          39    THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27  ANSWER 2 OF 11  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2004:563943  HCAPLUS
DOCUMENT NUMBER:          141:236934
TITLE:                    Inhibitor κB kinase is involved in the paracrine
                          crosstalk between human fat and muscle cells
AUTHOR(S):                Dietze, D.; Ramrath, S.; Ritzeler, O.;
                          Tennagels, N.; Hauner, H.; Eckel, J.
CORPORATE SOURCE:         Department of Clinical Biochemistry and
                          Pathobiochemistry, German Diabetes Research Institute,
```

Duesseldorf, Germany
SOURCE: International Journal of Obesity (2004), 28(8), 985-992
CODEN: IJOBDP; ISSN: 0307-0565
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB OBJECTIVE: Adipose tissue is now considered as an endocrine and secretory organ, and some adipocyte factors are thought to play a major role in the induction of insulin resistance in skeletal muscle. Here we tested the hypothesis that the crosstalk between fat and muscle involves activation of inhibitor κB Kinase (IKK) in the myocytes. MEASUREMENTS: Adipocyte-conditioned culture medium was added to the muscle cells overnight, or human fat and muscle cells were kept in coculture. Insulin signaling was subsequently analyzed in the myocytes. Involvement of IKK was assessed using I229, a highly specific inhibitor of the IKK complex. RESULTS: Adipocyte-conditioned medium strongly inhibited insulin-induced serine phosphorylation of Akt in myocytes with a rapid parallel activation of the nuclear factor KcB pathway in these cells. Conditioned medium lacking the perturbation of insulin signaling did not activate NF-κB. Insulin signaling to Akt was completely abrogated under co-culture conditions. The IKK inhibitor I229 did not affect protein expression of Akt, but fully restored insulin action in myocytes subjected to co-culture. CONCLUSION: These data show that the release of fat cell factors may rapidly induce insulin resistance in human skeletal muscle cells. This process appears to be mediated by an IKK/NF-κB dependent pathway. We suggest that inhibitors of IKK would be of use to counteract the neg. crosstalk between fat and muscle.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 3 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:314781 HCAPLUS
DOCUMENT NUMBER: 141:1810

TITLE: Adiponectin counteracts cytokine- and fatty acid-induced apoptosis in the pancreatic beta-cell line INS-1

AUTHOR(S): Rakatzi, I.; Mueller, H.; **Ritzeler, O.**; Tennagels, N.; Eckel, J.
CORPORATE SOURCE: Department of Clinical Biochemistry and Pathobiochemistry, German Diabetes Research Institute, Duesseldorf, Germany

SOURCE: Diabetologia (2004), 47(2), 249-258
CODEN: DBTGAJ; ISSN: 0012-186X
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Pancreatic beta-cell apoptosis is a common feature of Type 1 and Type 2 diabetes and leptin exerts an anti-apoptotic function in these cells. The beta-cell line INS-1 was used to test the hypothesis that the adipocyte hormone adiponectin might mediate an anti-apoptotic effect comparable to leptin. Apoptosis was induced by culturing cells with a cytokine combination (interleukin-1β/interferon-γ) or palmitic acid in absence or presence of leptin or the globular domain of adiponectin (gAcrp30), resp. INS-1 cells had a prominent sensitivity towards cytokine- and fatty acid-induced apoptosis, resulting in about three- and six-fold increases in caspase 3 activation and DNA fragmentation, resp. The gAcrp30 strongly (50-60%) inhibited palmitic acid-induced apoptosis, with a weaker effect against cytokine-induced apoptosis (35%). The same result was observed for leptin with both adipokines being non-additive.

Reduction of apoptosis by an inhibitor of IκB-kinase (IKK) indicated the involvement of the nuclear factor (NF)-κB pathway in both cytokine- and fatty acid-induced apoptosis, however, leptin and gAcrp30 were unable to block NF-κB activation. Cytokine- and fatty-acid-induced suppression of glucose/forskolin-stimulated insulin secretion was completely prevented through the action of gAcrp30, whereas leptin was only effective against lipotoxicity-mediated beta-cell dysfunction. Thus, the authors' data show that gAcrp30 partially rescues beta cells from cytokine- and fatty-acid-induced apoptosis and completely restores autoimmune- and lipotoxicity-induced dysfunction of insulin-producing cells. The authors suggest that gAcrp30 exerts its anti-apoptotic function without modulating NF-κB activation. This novel beta cell protective function of gAcrp30 might serve to counteract autoimmune- and lipotoxicity-induced beta-cell destruction.

REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 4 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:184390 HCAPLUS
DOCUMENT NUMBER: 140:399866
TITLE: Specific inhibition of IκB kinase reduces hyperalgesia in inflammatory and neuropathic pain models in rats
AUTHOR(S): Tegeder, Irmgard; Niederberger, Ellen; Schmidt, Ronald; Kunz, Susanne; Guehring, Hans; **Ritzeler, Olaf**; Michaelis, Martin; Geisslinger, Gerd
CORPORATE SOURCE: Pharmazentrum frankfurt, Institut fuer Klinische Pharmakologie, Klinikum der Johann Wolfgang Goethe-Universitaet Frankfurt, Frankfurt, 60590, Germany
SOURCE: Journal of Neuroscience (2004), 24(7), 1637-1645
CODEN: JNRSDS; ISSN: 0270-6474
PUBLISHER: Society for Neuroscience
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Phosphorylation of IκB through IκB kinase (IKK) is the first step in nuclear factor κB (NF-κB) activation and upregulation of NF-κB-responsive genes. Hence, inhibition of IKK activity may be expected to prevent injury-, infection-, or stress-induced upregulation of various proinflammatory genes and may thereby reduce hyperalgesia and inflammation. In the present study, we tested this hypothesis using a specific and potent IKK inhibitor (S1627). In an IKK assay, S1627 inhibited IKK activity with an IC50 value of 10.0 ± 1.2 nM. In cell culture expts., S1627 inhibited interleukin (IL)-1β-stimulated nuclear translocation and DNA-binding of NF-κB. Plasma concentration time courses after i.p. injection revealed a short half-life of 2.8 h in rats. Repeated i.p. injections were, therefore, chosen as the dosing regimen. S1627 reversed thermal and mech. hyperalgesia at 3 + 30 mg/kg in the zymosan-induced paw inflammation model and reduced the inflammatory paw edema at 3 + 40 mg/kg. S1627 also significantly reduced tactile and cold allodynia in the chronic constriction injury model of neuropathic pain at 30 mg/kg once daily. The drug had no effect on acute inflammatory nociception in the formalin test and did not affect responses to heat and tactile stimuli in naive animals. As hypothesized, S1627 prevented the zymosan-induced nuclear translocation of NF-κB in the spinal cord and the upregulation of NF-κB-responsive genes including cyclooxygenase-2, tumor necrosis factor-α, and IL-1β. Our data indicate that IKK may prove an interesting novel drug target in the treatment of pathol. pain and inflammation.

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

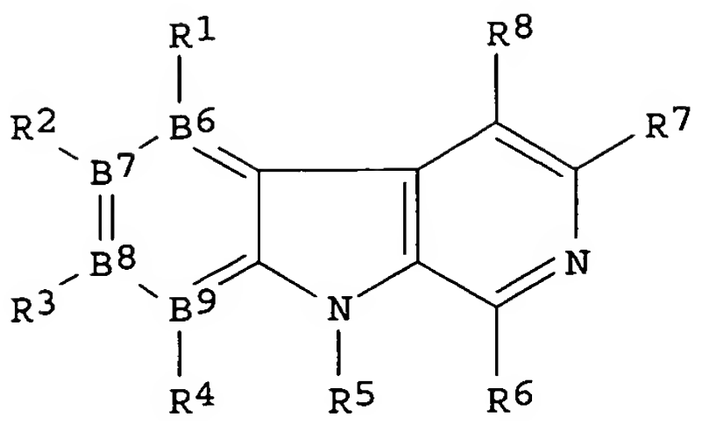
L27 ANSWER 5 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:405760 HCAPLUS
DOCUMENT NUMBER: 137:6093
TITLE: Preparation of substituted beta-carbolines as potential therapeutics in diseases associated with increased IκB kinase activity
INVENTOR(S): **Ritzeler, Olaf**; Castro, Alfredo; Grenier, Louis; Soucy, Francois; Hancock, Wayne W.; Mazdiyasni, Hormoz; Palombella, Vito; Adams, Julian
PATENT ASSIGNEE(S): Aventis Pharma Deutschland GmbH, Germany
SOURCE: Eur. Pat. Appl., 56 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1209158	A1	20020529	EP 2000-125169	20001118
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
CA 2402549	AA	20010920	CA 2001-2402549	20010228
WO 2001068648	A1	20010920	WO 2001-EP2237	20010228
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 2001037418	A5	20010924	AU 2001-37418	20010228
BR 2001009161	A	20021126	BR 2001-9161	20010228
EP 1268477	A1	20030102	EP 2001-909799	20010228
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003527394	T2	20030916	JP 2001-567739	20010228
EE 200200523	A	20040415	EE 2002-523	20010228
NZ 521386	A	20040625	NZ 2001-521386	20010228
US 2002099068	A1	20020725	US 2001-812785	20010315
US 6627637	B2	20030930		
NO 2002004338	A	20021105	NO 2002-4338	20020911
US 2004110759	A1	20040610	US 2003-627978	20030728

PRIORITY APPLN. INFO.:

EP 2000-105514	A	20000315
EP 2000-125169	A	20001118
WO 2001-EP2237	W	20010228
US 2001-812785	A1	20010315

OTHER SOURCE(S): MARPAT 137:6093
GI



I

AB Carbolines I (B6, B7, B8, B9 = C, N, no more than 2 N's at the same time; R1-R4, R8 = H, halogen, OH, CN, sulfo, NO2, alkoxy, substituted amino, substituted amide, CO2H, substituted hydroxy, ketone, ester, aryl, O-aryl, substituted aryl, O-substituted aryl, alkyl, substituted alkyl, CF3, CF2CF3; R5 = H, alkyl, alkyl radical, ketone, sulfo; R6, R7 = H, halogen, OH, Me, O-alkyl, O-substituted alkyl, substituted amino) were prepared as potential therapeutics for diseases associated with increased activity of IκB kinase. Thus, norharmane was treated with bromine to give 7-bromo-β-carboline (II). II had an IC50 value of 0.4 μM in a IκB kinase in an assay using IκB kinase complex prepared from HeLa S3 cell exts.

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 6 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:691768 HCAPLUS
DOCUMENT NUMBER: 135:242149
TITLE: Preparation of substituted β-carbolines as IκB kinase inhibitors
INVENTOR(S): **Ritzeler, Olaf**; Castro, Alfredo; Grenier, Louis; Soucy, Francois
PATENT ASSIGNEE(S): Aventis Pharma Deutschland G.m.b.H., Germany
SOURCE: Eur. Pat. Appl., 47 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1134221	A1	20010919	EP 2000-105514	20000315
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
CA 2402549	AA	20010920	CA 2001-2402549	20010228
WO 2001068648	A1	20010920	WO 2001-EP2237	20010228
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 2001037418	A5	20010924	AU 2001-37418	20010228
BR 2001009161	A	20021126	BR 2001-9161	20010228

EP 1268477	A1	20030102	EP 2001-909799		20010228
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
JP 2003527394	T2	20030916	JP 2001-567739		20010228
EE 200200523	A	20040415	EE 2002-523		20010228
NZ 521386	A	20040625	NZ 2001-521386		20010228
US 2002099068	A1	20020725	US 2001-812785		20010315
US 6627637	B2	20030930			
NO 2002004338	A	20021105	NO 2002-4338		20020911
ZA 2002007324	A	20030707	ZA 2002-7324		20020912
US 2004110759	A1	20040610	US 2003-627978		20030728
PRIORITY APPLN. INFO.:			EP 2000-105514	A	20000315
			EP 2000-125169	A	20001118
			WO 2001-EP2237	W	20010228
			US 2001-812785	A1	20010315

OTHER SOURCE(S): MARPAT 135:242149
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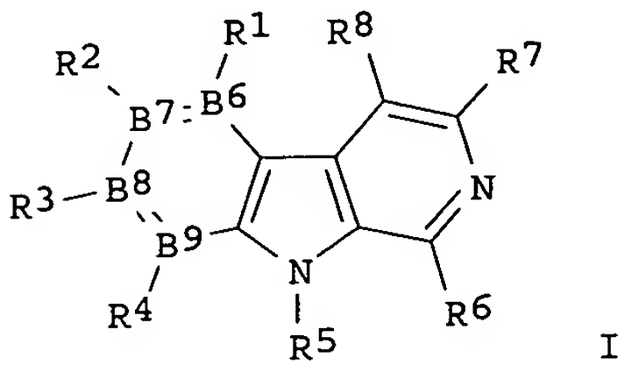


I

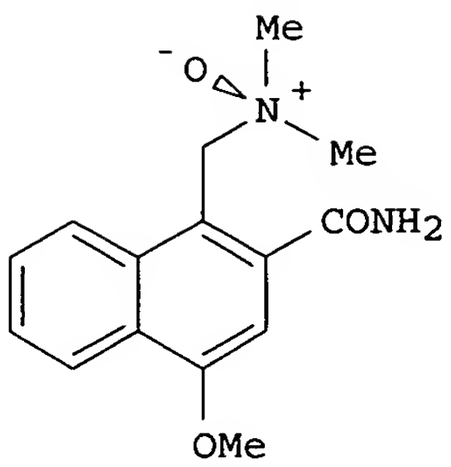
AB The title compds. [I; B6-B9 = C, N (no more than 2 N atoms at the same time); R1-R4, R8 = H, halo, OH, etc.; R5 = H, (un)substituted alkyl, etc.; R6, R7 = H, halo, OH, etc.], useful for prophylaxis and therapy of disorders in which increased activity of NFκB is involved such as asthma, osteoarthritis, rheumatoid arthritis, Alzheimer's disease, carcinomatous disorders and cardiac infarct, were prepared Thus, treating norharmane with Br2 in THF afforded 7-bromo-β-carboline which showed IC50 of 0.4 μM against IκB kinase.

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 7 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER:	2000:243728 HCAPLUS
DOCUMENT NUMBER:	133:4364
TITLE:	Atropisomeric transition state analogs
AUTHOR(S):	**Ritzeler, Olaf**; Parel, Serge; Therrien, Bruno; Bensel, Nicolas; Reymond, Jean-Louis; Schenk, Kurt
CORPORATE SOURCE:	Department of Chemistry and Biochemistry, University of Bern, Bern, CH-3012, Switz.
SOURCE:	European Journal of Organic Chemistry (2000), (7), 1365-1372 CODEN: EJOCFK; ISSN: 1434-193X
PUBLISHER:	Wiley-VCH Verlag GmbH
DOCUMENT TYPE:	Journal
LANGUAGE:	English

GI



I

AB Transition state mimicry is one of the most powerful concepts in enzyme inhibitor design and has led to the development of catalytic antibodies. Transition state analogs are compds. with a fixed shape that resemble the geometry and charge distribution of the transition state of a given reaction. Stabilization of a transition state like conformation is most often achieved by incorporating a ring system into the analog. We show herein that atropisomerism can be used as a new principle for enforcing a transition state like conformation. Atropisomerism relates to the existence of stereoisomers of structurally constrained mols. due to a frozen rotation about a single bond, as for example in binaphthol. The 1-aminomethylnaphthalene derivative I1 exhibits atropisomerism due to a frozen rotation about the C(1)-C(methylene) single bond, which holds the dihedral angle θ[C(2)-C(1)-C(methylene)-N] close to 90°. Compound I mimics the transition state for hydride transfer between 1,4-dihydroquinolines and acetone.

REFERENCE COUNT: 77 THERE ARE 77 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 8 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:703217 HCAPLUS
DOCUMENT NUMBER: 132:20324
TITLE: Atropisomeric transition state analogs
AUTHOR(S): **Ritzeler, Olaf**; Klein, Gerard; Reymond, Jean-Louis
CORPORATE SOURCE: Department of Chemistry & Biochemistry, University of Bern, Bern, 3012, Switz.
SOURCE: Phosphorus, Sulfur and Silicon and the Related Elements (1999), 144-146, 243-246
CODEN: PSSLEC; ISSN: 1042-6507
PUBLISHER: Gordon & Breach Science Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 11 refs. Atropisomerism is shown to be a useful design element for transition state analogs. A hydride transfer reaction between dihydroquinolines and ketones was mimicked using 1-substituted 2-naphthoamide derivs.
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

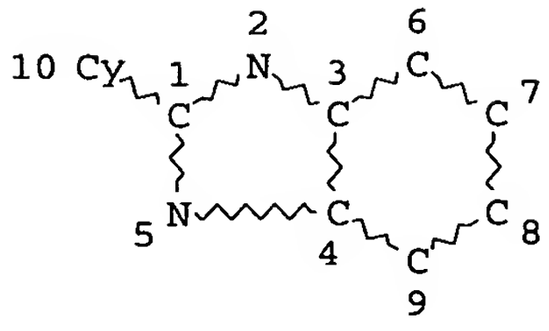
L27 ANSWER 9 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:262965 HCAPLUS
TITLE: Search for new moenomycin structure-activity relationships. Synthesis of a trisaccharide precursor of a moenomycin analog
AUTHOR(S): **Ritzeler, Olaf**; Hennig, Lothar; Findeisen, Matthias; Welzel, Peter; Muller, Dietrich

SOURCE: Tetrahedron (1997), 53(15), 5357
CODEN: TETRAB; ISSN: 0040-4020
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal; Errata
LANGUAGE: English
AB Unavailable

L27 ANSWER 10 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:105492 HCAPLUS
DOCUMENT NUMBER: 126:199768
TITLE: Synthesis of trisaccharide analog of monoenomycin A12. Implications of new moenomycin structure-activity relationships
AUTHOR(S): **Ritzeler, Olaf**; Hennig, Lothar; Findeisen, Matthias; Welzel, Peter; Mueller, Dietrich; Markus, Astrid; van Heijenoort, Jean
CORPORATE SOURCE: Fakultaet Chemie Mineralogie, Univ. Leipzig, Leipzig, D-04103, Germany
SOURCE: Tetrahedron (1997), 53(5), 1675-1694
CODEN: TETRAB; ISSN: 0040-4020
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A trisaccharide analog of moenomycin A, has been synthesized and has found to be antibiotically inactive. A binding model for moenomycin-type transglycosylase inhibitors at the enzyme penicillin binding protein is proposed.
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 11 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:105490 HCAPLUS
DOCUMENT NUMBER: 126:199767
TITLE: Search for new moenomycin structure-activity relationships. Synthesis of a trisaccharide precursor of a moenomycin analog
AUTHOR(S): **Ritzeler, Olaf**; Hennig, Lothar; Findeisen, Matthias; Welzel, Peter; Mueller, Dietrich
CORPORATE SOURCE: Fakultaet Chemie Mineralogie, Univ. Leipzig, Leipzig, D-04103, Germany
SOURCE: Tetrahedron (1997), 53(5), 1665-1674
CODEN: TETRAB; ISSN: 0040-4020
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB On the way to a trisaccharide analog of the antibiotic moenomycin A a trisaccharide intermediate has been prepared making use of a combination of Danishefsky's sulfonamido-glycosidation and the Schmidt trichloroacetimidate procedure.
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> => d stat que l35
L1 STR



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DEFAULT ECLEVEL IS LIMITED

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NUMBER OF NODES IS 10

STEREO ATTRIBUTES: NONE
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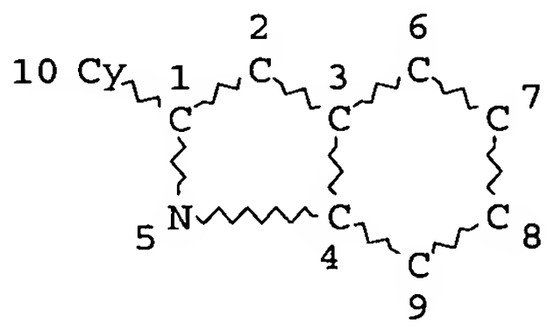

NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
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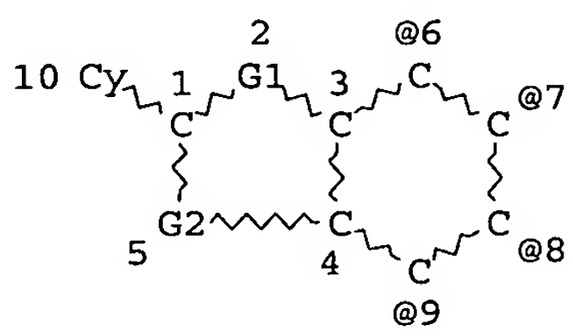

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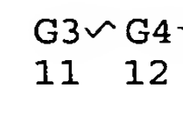

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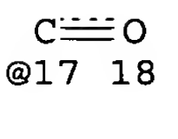
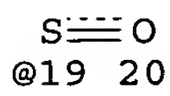


C=O
@17 18



S=O
@19 20

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VAR G2=NH/15
VAR G3=6/7/8/9
VAR G4=17/19
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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
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STEREO ATTRIBUTES: NONE
L5          3405 SEA FILE=REGISTRY SUB=L3 SSS FUL L4
L6           206 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L5
L7             6 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L6 AND (PAIN OR HEADACHE OR
                 MIGRAINE OR CEPHALA? OR ?HERPES? OR ?ZOSTER? OR ?NEURALG?)
L13         7274 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ?KAPPA?(L)KINASE
L14            5 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L13 AND L6
L15            3 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L14 NOT L7
L21       102269 SEA FILE=HCAPLUS ABB=ON  PLU=ON  PAIN+ALL/CV
L22            6 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L6 AND L21
L23            1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L22 NOT L7
L24            4 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L15 OR L23
L25          104 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "MICHAELIS M"/AU OR "MICHAELIS
                  M L"/AU OR "MICHAELIS MARTIN"/AU OR "MICHAELIS MARTIN L"/AU
L26           16 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ("RITZELER O"/AU OR "RITZELER
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L27           11 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L26 NOT (L7 OR L24)
L28           64 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "JAEHNE G"/AU OR "JAEHNE
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L29          185 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ("GEISSLINGER G"/AU OR
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L30           87 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ("SCHAIBLE H G"/AU OR
                 "SCHAIBLE HANS GEORG"/AU)
L31            1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L25 AND L28 AND L29 AND L30
L32            6 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L25 AND (L28 OR L29 OR L30)
L33            1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L28 AND (L29 OR L30)
L34            5 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L29 AND L30
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                 NOT (L7 OR L24 OR L27)


=> d ibib abs l35 1-8

L35  ANSWER 1 OF 8  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2005:59905  HCAPLUS
DOCUMENT NUMBER:          142:127615
TITLE:                    Sequences of human calpains for screening calpain
                          inhibitors that modulate pain
INVENTOR(S):              Michaelis, Martin; Geisslinger, Gerd
                          ; Niederberger, Ellen
PATENT ASSIGNEE(S):       Aventis Pharma Deutschland G.m.b.H., Germany
SOURCE:                   U.S. Pat. Appl. Publ., 24 pp.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.          KIND   DATE        APPLICATION NO.          DATE
     ----------------    ----   --------    ---------------------    --------
     US 2005014182        A1    20050120    US 2004-886451           20040707
     DE 10331980          A1    20050217    DE 2003-10331980         20030714
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WO 2005004905 A1 20050120 WO 2004-EP7083 20040630
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: DE 2003-10331980 A 20030714
US 2003-528375P P 20031210

AB The invention relates to the use of calpain or functional fragments or derivs. thereof for the preparation of pharmaceutical compds. that modulate pain, and the use of calpain or functional fragments of derivs. thereof for identifying such compds., and a method of screening pharmaceuticals useful for modulating and/or preventing pain.

L35 ANSWER 2 OF 8 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:1054243 HCAPLUS
DOCUMENT NUMBER: 142:16844
TITLE: Use of 2-amino-1-3-propanediol derivatives for the manufacture of a medicament for the treatment of various types of pain
INVENTOR(S): **Michaelis, Martin; Geisslinger, Gerd** ; Scholich, Klaus
PATENT ASSIGNEE(S): Aventis Pharma Deutschland G.m.b.H., Germany
SOURCE: Eur. Pat. Appl., 18 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1484057	A1	20041208	EP 2003-12864	20030606
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
WO 2004110421	A1	20041223	WO 2004-EP5470	20040521
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004248988	A1	20041209	US 2004-853761	20040525

PRIORITY APPLN. INFO.: EP 2003-12864 A 20030606
US 2003-510994P P 20031014

OTHER SOURCE(S): MARPAT 142:16844

AB The present invention relates to the use of 2-amino-1,3-propanediol derivs. for the preparation of pharmaceuticals for the prophylaxis or treatment of pain. The analgesic effect of sphingosine 1-phosphate was determined in

rats.
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 3 OF 8 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:1035017 HCAPLUS
DOCUMENT NUMBER: 142:16806
TITLE: Use of PAM (protein associated with Myc) for control of cAMP and adenylate cyclase levels in the control of pain
INVENTOR(S): **Michaelis, Martin; Geisslinger, Gerd**; Scholich, Klaus; Tegeder, Irmgard
PATENT ASSIGNEE(S): Aventis Pharma Deutschland GmbH, Germany
SOURCE: Eur. Pat. Appl., 298 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1481685	A1	20041201	EP 2003-12388	20030530
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
WO 2004105785	A2	20041209	WO 2004-EP4513	20040429
WO 2004105785	A3	20050127		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2005032695	A1	20050210	US 2004-850591	20040520

PRIORITY APPLN. INFO.: EP 2003-12388 A 20030530
US 2003-520587P P 20031117

AB Fragments of the 510 kDa protein PAM (protein associated with Myc) that can alter intracellular cAMP or adenylate cyclase levels are identified for use in the development of novel analgesics. Induction of PAM mRNA in a zymosan model is demonstrated. PAM interacts with adenylate cyclases to inhibit activation by Gα proteins.
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 4 OF 8 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:1035015 HCAPLUS
DOCUMENT NUMBER: 142:28133
TITLE: Use of sphingosine-1-phosphate and PAM (protein associated with Myc) for the preparation of pharmaceutical compounds to treat or alleviate pain
INVENTOR(S): **Michaelis, Martin; Geisslinger, Gerd**; Scholich, Klaus
PATENT ASSIGNEE(S): Aventis Pharma Deutschland GmbH, Germany
SOURCE: Eur. Pat. Appl., 345 pp.
CODEN: EPXXDW

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1481680	A1	20041201	EP 2003-12389	20030530
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
WO 2004105773	A2	20041209	WO 2004-EP5236	20040515
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2005032744	A1	20050210	US 2004-850586	20040520
PRIORITY APPLN. INFO.:			EP 2003-12389 A	20030530
			US 2003-520780P P	20031117

AB The present invention is based on the discovery that sphingosine-1-phosphate (S1P) and PAM (protein associated with Myc) are involved in nociceptive processing and sensitization mechanisms within the spinal cord and dorsal root ganglia. PAM is expressed in sensory neurons of the spinal cord as well as in dorsal root ganglia of adult rats, acts to inhibit Gsα-stimulated adenylate cyclase, is up-regulated after nociceptive stimuli (formalin injection), and the nociceptive response is significantly increased when endogenous PAM expression in the spinal cord is decreased by antisense oligonucleotides. S1P influences PAM signaling in HeLa cells by inducing PAM translocation from the endoplasmic reticulum to the plasma membrane, thereby mediating long-term inhibition of adenylate cyclase. The analgesic effect of S1P in the spinal cord intrathecal application of exogenous S1P to the spinal cord, and known S1P receptor agonists demonstrate analgesic/antinociceptive effects. Thus, the invention provides S1P receptor agonists and, more specifically, FTY720 [(2-amino-2-(4-octylphenyl)ethyl)propane-1,3-diol] functional derivs. and analogs, to modulate, lessen, or abolish pain.

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 5 OF 8 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:269891 HCAPLUS
DOCUMENT NUMBER: 133:38123
TITLE: Inhibition of noxious stimulus-induced spinal prostaglandin E2 release by flurbiprofen enantiomers: a microdialysis study
AUTHOR(S): **Geisslinger, Gerd**; Muth-Selbach, Uta; Coste, Ovidiu; Vetter, Gregor; Schrodter, Andreas; **Schaible, Hans-Georg**; Brune, Kay; Tegeder, Irmgard
CORPORATE SOURCE: Zentrum der Pharmakologie, Klinikum der Johann Wolfgang Goethe-Universitat, Frankfurt am Main, 60590, Germany
SOURCE: Journal of Neurochemistry (2000), 74(5), 2094-2100
CODEN: JONRA9; ISSN: 0022-3042

PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Peripheral noxious stimuli have been shown to induce prostaglandin (PG) E2 release at the site of inflammation and in the spinal cord. The antiinflammatory and antinociceptive effects of cyclooxygenase-inhibiting drugs are thought to depend on the inhibition of PG synthesis. R-Flurbiprofen, however, does not inhibit cyclooxygenase activity in vitro but still produces antinociceptive effects. To find out whether R-flurbiprofen acts via inhibition of spinal PG release, concns. of PGE2 and flurbiprofen in spinal cord tissue were assessed by microdialysis. The catheter was transversally implanted through the dorsal horns of the spinal cord at level L4. R- and S-flurbiprofen (9 and 27 mg kg-1, resp.) were administered i.v. 10-15 min before s.c. injection of formalin into the dorsal surface of one hind-paw. Flurbiprofen was rapidly distributed into the spinal cord with maximal concns. after 30-45 min. Baseline PGE2 dialyzate concns. were 100.6 ± 6.4 pg ml-1 (mean ± SEM). After formalin injection they rose about threefold with a maximum of 299.4 ± 68.4 pg ml-1 at 7.5 min. After .apprx.1 h PGE2 levels returned to baseline. Both flurbiprofen enantiomers completely prevented the formalin-induced increase of spinal PGE2 release and reduced PGE2 concns. below basal levels. S- and R-flurbiprofen at 9 mg kg-1 produced a min. of 15.8 ± 5.2 and 27.7 ± 14.9 pg ml-1, resp., and 27 mg kg-1 S- and R-flurbiprofen resulted in 11.7 ± 1.7 and 9.3 ± 4.7 pg ml-1, resp. PGE2 levels remained at the min. up to the end of the observation period at 5 h. When 27 mg kg-1 R-flurbiprofen was injected i.v. without subsequent formalin challenge, baseline immunoreactive PGE2 concns. were not affected. S-Flurbiprofen (27 mg kg-1), however, led to a moderate reduction (.apprx.40%). The data suggest that antinociception produced by R-flurbiprofen is mediated at least in part by inhibition of stimulated spinal PGE2 release and support the current view that increased spinal PGE2 release significantly contributes to nociceptive processing.

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 6 OF 8 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:448843 HCAPLUS
DOCUMENT NUMBER: 129:197755
TITLE: The effects of S- and R-flurbiprofen on the inflammation-evoked intraspinal release of immunoreactive substance P-a study with antibody microprobes
AUTHOR(S): **Schaible, Hans-Georg**; Neugebauer, Volker; **Geisslinger, Gerd**; Beck, Ulrike
CORPORATE SOURCE: Physiologisches Institut, Universitat Wurzburg, Wurzburg, D-97070, Germany
SOURCE: Brain Research (1998), 798(1,2), 287-293
CODEN: BRREAP; ISSN: 0006-8993
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Using antibody coated microprobes in anesthetized rats, we studied the intraspinal release of immunoreactive substance P during development of kaolin/carrageenan-induced inflammation in the knee joint, and the effects of S- and R-flurbiprofen on inflammation-evoked intraspinal release of immunoreactive substance P once inflammation was established. During the first 6 h after induction of acute inflammation, the basal release and the release of immunoreactive substance P evoked by innocuous pressure applied to the knee showed increases (n=4 rats). An i.v. dose of 9 mg/kg S-flurbiprofen (a potent inhibitor of cyclooxygenases that is

anti-inflammatory and antinociceptive) did not significantly alter the pattern of inflammation-evoked release of immunoreactive substance P within 2 h although this dose reduced the responses of spinal cord neurons to pressure applied to the inflamed knee joint within 15 min to about 15% of the predrug value (Neugebauer et al., 1995). The subsequent i.v. injection of 27 mg/kg S-flurbiprofen significantly changed the pattern of release of immunoreactive substance P showing a reduction of the level of immunoreactive substance P in the dorsal horn within 1 h (n=4 rats). The release of immunoreactive substance P was also reduced after the i.v. injection of 27 mg/kg R-flurbiprofen that is also antinociceptive but less anti-inflammatory (n=5 rats). These data show that both S- and R-flurbiprofen reduce the inflammation-evoked intraspinal release of immunoreactive substance P within hours. However, the reduction of release of immunoreactive substance P does not seem to be a prerequisite for the initial antinociceptive action of non-steroidal anti-inflammatory drugs. It may be rather important in the long term range.

REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 7 OF 8 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:470381 HCAPLUS
DOCUMENT NUMBER: 125:157438
TITLE: New insights into the site and mode of antinociceptive action of flurbiprofen enantiomers
AUTHOR(S): **Geisslinger, Gerd; Schaible, Hans-Georg**
CORPORATE SOURCE: Department Experimental, University Erlangen, Erlangen, D-91054, Germany
SOURCE: Journal of Clinical Pharmacology (1996), 36(6), 513-520
CODEN: JCPCBR; ISSN: 0091-2700
PUBLISHER: Lippincott-Raven
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 85 refs. The S-enantiomer of flurbiprofen has been shown to have both antiinflammatory and antinociceptive effects, whereas R-flurbiprofen is antinociceptive but not antiinflammatory. Importantly, only S-flurbiprofen inhibited prostaglandin biosynthesis in vitro at therapeutic concns. R-flurbiprofen did not undergo significant chiral inversion to S-flurbiprofen in rats and humans. A study was conducted to gain new insight into the possible sites and modes of action of flurbiprofen enantiomers. In a modified Randall Selitto assay, both enantiomers were antinociceptive in a dose-dependent manner after systemic administration. After local administration into the inflamed paw, only S-flurbiprofen produced significant dose-related antinociception. In a physiol. study, the authors recorded extracellularly from nociceptive spinal cord neurons that were rendered hyperexcitable. I.v. administration of R- and S-flurbiprofen reduced responses of neurons to pressure applied to the inflamed knee and the noninflamed ankle and paw in a dose-dependent manner. When injected directly into the knee joint, only S-flurbiprofen but not R-flurbiprofen reduced responses to pressure. These results suggest a central site of antinociceptive action for R- and S-flurbiprofen and an addnl. peripheral site for S-flurbiprofen. The findings may be of clin. relevance, as it was demonstrated that both enantiomers also were antinociceptive in humans. Because R-flurbiprofen caused less toxicity in rats than the S-enantiomer or the racemic compound, a reduction in the quant. most important side effects in the gastrointestinal tract might be achieved with the use of R-flurbiprofen for pain therapy.

L35 ANSWER 8 OF 8 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1995:959281 HCAPLUS
DOCUMENT NUMBER: 124:21349
TITLE: Antinociceptive effects of R(-)- and S(+)-flurbiprofen on rat spinal dorsal horn neurons rendered hyperexcitable by an acute knee joint inflammation
AUTHOR(S): Neugebauer, Volker; **Geisslinger, Gerd**; Ruemenapp, Petra; Weiretter, Frank; Szelenyi, Istvan; Brune, Kay; **Schaible, Hans-Georg**
CORPORATE SOURCE: Department of Physiology, University of Wuerzburg, Wuerzburg, D-97070, Germany
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1995), 275(2), 618-28
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The antinociceptive effects of the S(+)-enantiomer of flurbiprofen (potent inhibitor of cyclooxygenase) and the R(-)-enantiomer (500 times less potent) were investigated in the spinal cord of 20 anesthetized rats. In lumbar segments, 20 wide-dynamic-range dorsal horn neurons with knee joint input were recorded extracellularly. After induction of an acute inflammation in the knee joint by kaolin and carrageenan, the neurons developed hyperexcitability consisting of enhanced responses to stimuli applied to the inflamed knee and the noninflamed ankle and an expansion of receptive fields. I.v. administration of R(-)-flurbiprofen (1-9 mg/kg) and S(+)-flurbiprofen (0.3-9 mg/kg) at 5.5 to 8.5 h after kaolin, dose dependently reduced the neurons' responses to pressure applied to the inflamed knee (18 of 18 neurons) and the noninflamed ankle (17 of 17 neurons) and paw (8 of 8 neurons). R(-)-flurbiprofen decreased the receptive field size in 8 of 16 neurons, S(+)-flurbiprofen in 10 of 16 neurons. The suppressive effects started 3 to 6 min and reached a maximum 9 to 15 min after i.v. administration. S(+)-flurbiprofen was more potent than the R(-)enantiomer. When injected directly into the knee joint, S(+)-flurbiprofen (50 and 80 μg), but not the R(-)-enantiomer (100 and 180 μg) reduced the hyperexcitability in 12 of 12 neurons. These results suggest a central site of antinociceptive action for R(-)-flurbiprofen and S(+)-flurbiprofen and an addnl. peripheral site for S(+)-flurbiprofen. The doses used in these expts. did not produce any sedative effects in rats subjected to behavioral testing.

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L1                STR
L2                STR
L3           100862 SEA FILE=REGISTRY SSS FUL L1 OR L2
L4                STR
L5             3405 SEA FILE=REGISTRY SUB=L3 SSS FUL L4
L6              206 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L5
L7                6 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L6 AND (PAIN OR HEADACHE OR
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L15               3 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L14 NOT L7
L21          102269 SEA FILE=HCAPLUS ABB=ON  PLU=ON  PAIN+ALL/CV
L22               6 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L6 AND L21
L23               1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L22 NOT L7
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                "GEISSLINGER GERD"/AU)
L30          87 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ("SCHAIBLE H G"/AU OR
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L31           1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L25 AND L28 AND L29 AND L30
L32           6 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L25 AND (L28 OR L29 OR L30)
L33           1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L28 AND (L29 OR L30)
L34           5 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L29 AND L30
L35           8 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L31 OR L32 OR L33 OR L34)
                NOT (L7 OR L24 OR L27)
L37         108 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ((L25 OR L28 OR L29 OR L30)
                AND PAIN) NOT (L7 OR L24 OR L27 OR L35)
L38          86 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L37 AND PD=<NOVEMBER 15, 2003

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L38  ANSWER 1 OF 86  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2003:584852  HCAPLUS
DOCUMENT NUMBER:          140:105017
TITLE:                    Peripheral and central antihyperalgesic effects of
                          diclofenac in a model of human inflammatory
                          pain
AUTHOR(S):                Burian, Maria; Tegeder, Irmgard; Seegel, Maic;
                          Geisslinger, Gerd
CORPORATE SOURCE:         Klinikum der Johann-Wolfgang-Goethe-Universitat
                          Frankfurt, Frankfurt/Main, Germany
SOURCE:                   Clinical Pharmacology & Therapeutics (St. Louis, MO,
                          United States) (2003), 74(2), 113-120
                          CODEN: CLPTAT; ISSN: 0009-9236
PUBLISHER:                Mosby, Inc.
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   Exptl. evidence suggests that the antihyperalgesic effect of nonsteroidal
     anti-inflammatory drugs may include both peripheral (inflammatory site)
     and central sites of action.  The aim of this study was to assess
     peripheral and central antihyperalgesic effects of diclofenac in a human
     exptl. pain model.  This was a randomized, double-blind,
     placebo-controlled study designed to compare the antihyperalgesic efficacy
     of topical (65 mg) and oral (93 mg) diclofenac via ests. of mech.
     pain thresholds obtained at the site of induced inflammation with
     von Frey hairs.  The dose of the 2 diclofenac formulations was calculated to
     achieve similar target concns., monitored in the inflammatory tissue by
     intradermal microdialysis.  Simultaneous serial blood samples were
     collected to determine the systemic concns. of the drug.  Diclofenac was
     superior to placebo 1 h after topical application (P < .002) and 1 to 3 h
     after oral intake (P < .016).  Topical diclofenac was more effective than
     oral diclofenac 1 h after dosing and produced higher tissue concns. (46.1
     ng/mL vs. 11.4 ng/mL, P < .02), whereas the compound was not detectable in
     plasma.  Oral diclofenac had a higher antihyperalgesic efficacy at later
     observation periods (2-2.5 h after dosing), when tissue concns. of
     diclofenac for the 2 treatments did not differ significantly.  The overall
     pain relief over a 3-h postdose period was 1.7-fold greater with
     oral diclofenac than with topical diclofenac.  However, the total tissue
     area under the curve after oral diclofenac did not exceed that for the
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topical formulation (32.2 ng · h · mL-1 vs. 40.7 ng · h · mL-1). The higher antihyperalgesic efficacy of oral diclofenac as compared with topical diclofenac at comparable tissue concns. suggests that not only peripheral but also central mechanisms are involved in the antihyperalgesic effects of systemically administered diclofenac.

REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 2 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:540154 HCAPLUS
DOCUMENT NUMBER: 139:208136
TITLE: Prostaglandin E2 increases the expression of the neurokinin1 receptor in adult sensory neurones in culture: A novel role of prostaglandins
AUTHOR(S): Segond von Banchet, Gisela; Scholze, Anita; **Schaible, Hans-Georg**
CORPORATE SOURCE: Institute of Physiology I, University of Jena, Jena, D-07740, Germany
SOURCE: British Journal of Pharmacology (**2003**), 139(3), 672-680
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Peripheral inflammation causes an increase in the proportion of primary afferent neurons that express neurokinin1 (NK1) receptors for substance P (SP). This upregulation may contribute to the neuronal mechanisms of inflammatory **pain.** The aim of this study was to identify endogenous mediators that stimulate upregulation of NK1 receptors in dorsal root ganglion (DRG) neurons. Cultured DRG neurons from the adult normal rat were exposed for 2 days to media that contained specific mediators, namely potassium in high concentration, prostaglandin E2 (PGE2), somatostatin (SRIF), and compds. influencing second messenger cascades. After fixation neurons were labeled with an NK1 receptor antibody. Repetitive addition of the inflammatory mediator PGE2 or dibutyryl-cyclic adenosine 3',5' monophosphate (db-cAMP) to the culture medium enhanced the proportion of neurons with NK1 receptor-like immunoreactivity from about 12% up to 40%. PGE2-induced upregulation was prevented by coadministration of PGE2 and a protein kinase A inhibitor or SRIF to the medium. High potassium concentration, protein kinase C inhibitors and omission of nerve growth factor from the medium had no effect. In calcium-imaging expts., bath application of SP evoked increases of the intracellular calcium concentration in about 20% of the neurons. This proportion increased to about 40% after PGE2-pretreatment, but the increase was prevented when PGE2 and SRIF were coadministered to the medium. These data show that the expression of NK1 receptor-like immunoreactivity in DRG neurons is regulated by the inflammatory mediator PGE2. This upregulation depends on the intracellular adenylyl cyclase - protein kinase A pathway.

REFERENCE COUNT: 62 THERE ARE 62 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 3 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:477961 HCAPLUS
DOCUMENT NUMBER: 140:26494
TITLE: Differential role of spinal prostaglandin receptor subtypes EP1-EP4 in rats with normal and inflamed knee joints
AUTHOR(S): Ebersberger, Andrea; Baer, Karl-Juergen; Teschner, Philipp; Telleria-Diaz, Alejandro; Vasquez, Enrique;

Schaible, Hans-Georg
CORPORATE SOURCE: Department of Physiology, University of Jena, Jena, Germany
SOURCE: Progress in Pain Research and Management (**2003**), 24(Proceedings of the 10th World Congress on Pain, 2002), 397-406
CODEN: PPRMFO
PUBLISHER: IASP Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The role of G-protein-coupled prostanoid (EP) receptors in spinal nociception, and the importance of these receptors under normal and inflammatory conditions were studied using topical application of recently developed specific agonists to the spinal cord of rats with normal and inflamed knee joints. Results show the importance of spinal hyperexcitability in the generation of inflammatory joint **pain**, and an interesting role of EP receptors in this process. Through the action of EP1, EP2, and EP4 receptors, prostaglandin E2 generates spinal hyperexcitability. However, once inflammation evoked hyperexcitability is established, PGE2 may actively attenuate its own effect by acting on EP3α receptors. Thus, spinal PGE2 has pronociceptive as well as antinociceptive effects, depending on the presence or absence of peripheral inflammation.
REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 4 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:328338 HCAPLUS
DOCUMENT NUMBER: 139:316311
TITLE: Review article: the pharmacological properties and clinical use of valdecoxib, a new cyclo-oxygenase-2-selective inhibitor
AUTHOR(S): Alsalameh, S.; Burian, M.; Mahr, G.; Woodcock, B. G.; **Geisslinger, G.**
CORPORATE SOURCE: Out-patient Clinic for Rheumatic Diseases, Marburg, Germany
SOURCE: Alimentary Pharmacology and Therapeutics (**2003**), 17(4), 489-501
CODEN: APTHEN; ISSN: 0269-2813
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Cyclo-oxygenase-2-selective inhibitors produce less gastric damage than conventional non-steroidal antiinflammatory drugs. Valdecoxib is a new orally administered cyclo-oxygenase-2-selective inhibitor, recently approved for use in osteoarthritis, rheumatoid arthritis and primary dysmenorrhea in the USA. The drug has been evaluated in more than 60 clin. studies involving more than 14 000 patients and healthy volunteers. The analgesic efficacy of valdecoxib at a dose of 10 mg once daily in both osteoarthritis and rheumatoid arthritis is superior to that of placebo and similar to that of traditional non-steroidal anti-inflammatory drugs. Valdecoxib is effective in single doses of up to 40 mg for the alleviation of acute menstrual **pain** and has a rapid onset of action (within 30 min) and a long duration of analgesia (up to 24 h). Valdecoxib is well tolerated and has safety advantages compared with traditional non-steroidal anti-inflammatory drugs in terms of less gastrointestinal toxicity and a lack of an effect on platelet function. The incidence of adverse effects involving the kidney (fluid retention, edema and hypertension) is similar to that of non-selective, nonsteroidal anti-inflammatory drugs.

REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 5 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:298418 HCAPLUS
DOCUMENT NUMBER: 139:159584
TITLE: G Protein-independent G1 Cell Cycle Block and Apoptosis with Morphine in Adenocarcinoma Cells: Involvement of p53 Phosphorylation
AUTHOR(S): Tegeder, Irmgard; Groesch, Sabine; Schmidtko, Achim; Haeussler, Annett; Schmidt, Helmut; Niederberger, Ellen; Scholich, Klaus; **Geisslinger, Gerd**
CORPORATE SOURCE: Klinische Pharmakologie, Pharmazentrum Frankfurt, Klinikum der Johann Wolfgang Goethe-Universitaet, Frankfurt am Main, 60590, Germany
SOURCE: Cancer Research (**2003**), 63(8), 1846-1852
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Opioid effects on tumor growth have been a controversial topic of discussion. In the present study, morphine inhibited tumor cell proliferation at concns. of ≥10 μM. This was primarily caused by inhibition of cell cycle progression from G to S phase. At higher concns. (≥500 μM for 24 h), morphine also caused cell death. In nude mice, morphine significantly reduced the growth of MCF-7 and MDA-MB231 tumors but had no effect on HT-29 tumor growth. In these expts., morphine plasma concns. were similar to those found in cancer patients receiving chronic morphine treatment for **pain** relief (0.9-3.4 μM). In MCF-7 and MDA-MB231 cells, morphine caused a naloxone (Nx)- and pertussis toxin-sensitive, concentration-dependent increase of GTPase activity, indicating that morphine signals could be transduced by opioid receptors via a G protein. However, the antiproliferative effects of morphine were not antagonized by Nx, pertussis toxin, forskolin, and 8-bromo-cAMP, suggesting that the typical opioid receptor-coupled signaling cascade involving the Gi, adenylyl cyclase, and protein kinase A was not involved. Instead, morphine caused an NH2-terminal phosphorylation of p53 at Ser9 and/or Ser15 and a stabilization of p53 in MCF-7 cells that express wild-type p53. p53 phosphorylation was not antagonized by Nx and resulted in an increase of p53-dependent proteins including p21, Bax, and the death receptor Fas. Blockade of Fas by Fas-fusion protein or inhibition of caspase 8 resulted in a partial inhibition of morphine-induced apoptosis. In addition, Fas ligand only induced apoptosis when administered together with morphine. However, the sensitivity of the tumor cells toward Fas ligand remained low. HT-29 cells, which express dominant neg. p53 and show no increase of GTPase activity when treated with morphine, were less sensitive in vitro and were not affected in vivo. Our results suggest that morphine, alone or in combination with Nx, may reduce the growth of certain tumors, apparently in part through activation of p53.
REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 6 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:223112 HCAPLUS
DOCUMENT NUMBER: 139:95051
TITLE: Opposite effects of rofecoxib on nuclear factor-κB and activating protein-1 activation
AUTHOR(S): Niederberger, Ellen; Tegeder, Irmgard; Schafer, Christine; Seegel, Maic; Grosch, Sabine;

Geisslinger, Gerd
CORPORATE SOURCE: Pharmazentrum frankfurt, Klinikum der Johann Wolfgang Goethe-Universitat Frankfurt, Frankfurt am Main, Germany
SOURCE: Journal of Pharmacology and Experimental Therapeutics (**2003**), 304(3), 1153-1160
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Rofecoxib is a selective cyclooxygenase (COX)-2 inhibitor approved for the treatment of **pain** and inflammation in rheumatoid and osteoarthritis. Daily doses between 12.5 and 50 mg were found to reduce **pain** and inflammation, however, without a clear dose-effect relation. Interestingly, rofecoxib treatment is associated with an unexpected incidence of renal adverse events compared with other COX inhibitors. Here, the effects of rofecoxib on the transcription factors nuclear factor-κB (NF-κB) and activating protein-1 (AP-1) were analyzed to find out whether transcriptional changes might explain the lack of clear dose dependency and the occurrence of renal side effects. In vitro, rofecoxib dose dependently inhibited DNA binding capacity of NF-κB at doses of 10 to 100 μM, whereas the binding activity of AP-1 was considerably increased at 100 μM. In vivo, the anti-inflammatory effect of rofecoxib was equal at 1 and 10 mg/kg, whereas 50 mg/kg caused a significant further reduction of a zymosan-induced paw edema. This was associated with a clear decrease of inducible nitric oxide synthase (iNOS) protein expression in the spinal cord at this dose. At 1 and 10 mg/kg, however, iNOS was increased but COX-2 was decreased. Thus, the expression of proinflammatory proteins was similarly inconsistent as transcription factor regulation. In conclusion, the opposite effects of rofecoxib on AP-1 and NF-κB may explain the lack of clear dose dependency with rofecoxib in clin. studies or animal expts. The effects on AP-1 may possibly affect renal sodium transport because certain renal sodium channels are regulated through AP-1. Transcription factor regulation might therefore influence both wanted and unwanted effects of rofecoxib.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 7 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:166413 HCAPLUS
DOCUMENT NUMBER: 138:383395
TITLE: Inhibition of cyclic guanosine 5'-monophosphate-dependent protein kinase I (PKG-I) in lumbar spinal cord reduces formalin-induced hyperalgesia and PKG upregulation
AUTHOR(S): Schmidtko, Achim; Ruth, Peter; **Geisslinger, Gerd**; Tegeder, Irmgard
CORPORATE SOURCE: Pharmazentrum Frankfurt, Klinikum der Johann Wolfgang Goethe-Universitat, Frankfurt am Main, 60590, Germany
SOURCE: Nitric Oxide (**2003**), 8(2), 89-94
CODEN: NIOXF5; ISSN: 1089-8603
PUBLISHER: Elsevier Science
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Nitric oxide-mediated nociception has been suggested to involve formation of cyclic guanosine 5'-monophosphate (cGMP) and activation of cGMP-dependent protein kinase (PKG). To further evaluate this pathway the authors assessed the effects of the PKG-inhibiting cGMP analog

Rp-8-Br-cGMPS in the rat formalin assay and analyzed the regulation of PKG expression in rat lumbar spinal cord. Spinally delivered Rp-8-Br-cGMPS (0.1-0.5 μmol i.t.) reduced the nociceptive behavior in a dose-dependent manner. Similar effects were achieved with Rp-8-Br-PET-cGMPS (0.5 μmol i.t.), another PKG-inhibitory cGMP analog. In contrast, Rp-8-Br-cAMPS (0.5 μmol i.t.), an inhibitor of protein kinase A, had no effect in this model. Formalin treatment resulted in a rapid (within 1 h), long-lasting (up to 96 h) upregulation of PKG-I protein expression. This increase was prevented in animals pretreated with Rp-8-Br-cGMPS (0.5 μmol i.t.) or morphine (2.5-5 mg/kg i.p.) 10 min prior to formalin injection. Spinal delivery of 8-Br-cGMP, a PKG-activating cGMP analog, without subsequent formalin treatment also caused an increase of PKG-I protein expression. Hence, the upregulation of PKG-I might possibly be mediated by cGMP itself. The authors' data suggest that PKG-I activation is involved in the synaptic transmission of nociceptive stimuli in the spinal cord and that PKG-I inhibitors might be interesting novel drugs for **pain** treatment.

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 8 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:136356 HCAPLUS
DOCUMENT NUMBER: 139:224250
TITLE: Analgesic effects of morphine and morphine-6-glucuronide in a transcutaneous electrical **pain** model in healthy volunteers
AUTHOR(S): Skarke, Carsten; Darimont, Jutta; Schmidt, Helmut; **Geisslinger, Gerd**; Loetsch, Joern
CORPORATE SOURCE: pharmazentrum frankfurt, Institute of Clinical Pharmacology, Johann Wolfgang Goethe University, Frankfurt, Germany
SOURCE: Clinical Pharmacology & Therapeutics (St. Louis, MO, United States) (**2003**), 73(1), 107-121
CODEN: CLPTAT; ISSN: 0009-9236
PUBLISHER: Mosby, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Objective: Our objective was to quantify the extent and time course of the effects of morphine-6-glucuronide and morphine on **pain** threshold, **pain** tolerance, pupil diameter, and side effects. Methods: In a double-blind, placebo-controlled, randomized, 3-way crossover study, 12 healthy volunteers (6 men and 6 women) received 63 to 112 mg of morphine-6-glucuronide or 26 to 66 mg of morphine as an i.v. bolus, followed by an infusion of the same medication for 1.8 to 6.4 h. Analgesia was assessed every 30 min for up to 16 h by means of transcutaneous elec. stimulation (sine wave, 5 Hz; intensity, 0-9.99 mA). Pupil diameter and side effects were recorded concomitantly. Results: At the administered doses, morphine-6-glucuronide and morphine had comparable effects on **pain** tolerance, pupil diameter, and side effects. The delay between the time course of the plasma concns. and the time course of the effects was longer for morphine-6-glucuronide than for morphine (transfer half-life, 8.2 h vs. 2.6 h for **pain** tolerance and 7.7 h vs. 2.8 h for pupil diameter). The slope of the linear concentration vs. effect relationship for **pain** tolerance was flatter for morphine-6-glucuronide than for morphine (0.05% vs. 0.6% increase in **pain** tolerance per nmol per L of morphine-6-glucuronide and morphine at effect site, resp.). Morphine-6-glucuronide was less potent than morphine in producing pupil constriction (mean concentration at half-maximum

effect, 745 nmol/L vs. 26.4 nmol/L for morphine-6-glucuronide and morphine, resp.). In carriers of the mutated G118 allele of the μ-opioid receptor, the potency of the pupil-constricting effects of morphine-6-glucuronide and morphine was significantly smaller, and carriers of the G11S allele reported less nausea and vomited less often after administration of morphine-6-glucuronide. Conclusions: Morphine-6-glucuronide clearly produced analgesic effects in healthy volunteers. However, the high amts. of systemic morphine-6-glucuronide needed to produce the same effects as morphine suggest that morphine-6-glucuronide barely contributes to the central nervous opioid effects after administration of analgesic doses of morphine.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 9 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:52840 HCAPLUS
DOCUMENT NUMBER: 138:332045
TITLE: Modulation of spinal nociceptive processing through the glutamate transporter GLT-1
AUTHOR(S): Niederberger, E.; Schmidtko, A.; Rothstein, J. D.; **Geisslinger, G.**; Tegeder, I.
CORPORATE SOURCE: Pharmazentrum Frankfurt, Klinikum der Johann Wolfgang Goethe-Universitat Frankfurt, Frankfurt am Main, 60590, Germany
SOURCE: Neuroscience (Oxford, United Kingdom) (**2003**), 116(1), 81-87
CODEN: NRSCDN; ISSN: 0306-4522
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB GLT-1 is the predominant glutamate transporter in most brain regions and therefore plays a major role in terminating synaptic transmission and protecting neurons from glutamate neurotoxicity. In the present study the authors assessed (i) the regulation of GLT-1 expression in the spinal cord after peripheral nociceptive stimulation and (ii) the nociceptive behavior of rats following inhibition or transient knockdown of spinal GLT-1. Formalin injection into one hindpaw caused a rapid transient upregulation of GLT-1 protein expression in the spinal cord which did not occur when rats were pretreated with morphine (10 mg/kg, i.p.) suggesting that the nociceptive input specifically caused the increase of GLT-1 transcription. Inhibition of GLT-1 by the transportable inhibitor trans-pyrrolidine-2,4-dicarboxylic acid resulted in a significant reduction of nociceptive behavior in the rat formalin assay. Similar results were obtained with a transient reduction of GLT-1 protein expression by antisense oligonucleotides. These data suggest that inhibition of GLT-1 activity or expression reduces excitatory synaptic efficacy and thereby nociception. Mechanisms that might explain this phenomenon may include activation of inhibitory metabotropic glutamate receptors, postsynaptic desensitization or disturbance of glutamate recycling.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 10 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:834086 HCAPLUS
DOCUMENT NUMBER: 138:120556
TITLE: What happens in the head? Migraine, cluster and stress headache
AUTHOR(S): **Schaible, Hans-Georg**; Ebersberger, Andrea
CORPORATE SOURCE: Institut fuer Physiologie - Neurophysiologie, Jena, D-07740, Germany

SOURCE: Pharmazie in Unserer Zeit (2002), 31(5), 452-457
CODEN: PHUZBI; ISSN: 0048-3664
PUBLISHER: Wiley-VCH Verlag GmbH & Co. KGaA
DOCUMENT TYPE: Journal; General Review
LANGUAGE: German

AB A review on classification and diagnostic criteria for headache disorders, the trigeminovascular system, and clin. symptoms and pathophysiol. of migraine, cluster headache, and stress headache. Dysfunction of the nociceptive system is discussed to be a cause of these **pain** diseases.

REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 11 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:787776 HCAPLUS
DOCUMENT NUMBER: 138:314430
TITLE: Dual effects of spinally delivered 8-bromo-cyclic guanosine mono-phosphate (8-bromo-cGMP) in formalin-induced nociception in rats
AUTHOR(S): Tegeder, Irmgard; Schmidtko, Achim; Niederberger, Ellen; Ruth, Peter; **Geisslinger, Gerd**
CORPORATE SOURCE: Pharmazentrum Frankfurt, Klinikum der Johann Wolfgang Goethe-Universitat, Frankfurt am Main, 60590, Germany
SOURCE: Neuroscience Letters (**2002**), 332(2), 146-150
CODEN: NELED5; ISSN: 0304-3940
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The rat formalin assay was used to assess effects of the cyclic guanosine mono-phosphate (cGMP) analog, 8-bromo-cGMP on nociception and cGMP dependent protein kinase I (protein kinase G; PKG-I) expression in lumbar spinal cord. Intrathecal (i.t.) delivery of low doses of 8-bromo-cGMP (0.1-0.25 μmol) reduced nociceptive behavior and formalin-induced upregulation of PKG-I in the spinal cord. Medium doses (0.5-1 μmol i.t.) had no effect and high doses (2.5 μmol i.t.) caused hyperalgesia associated with a further increase of PKG-I expression and a PKG-I clip. To explain these dose-dependent contrary effects we assessed the potential involvement of various cGMP targets: protein kinase G, cyclic nucleotide gated cation channels (CNGs), phosphodiesterases (PDE2 and PDE3) and AMPA-receptors. The PKG inhibitor, Rp-8-bromo-cGMPS did not antagonize the antinociceptive effects of 8-bromo-cGMP but caused antinociception itself. Inhibitors of CNGs, PDE2 and PDE3 had no effect on formalin evoked nociceptive behavior. S-AMPA however, antagonized the antinociceptive effects of 8-bromo-cGMP. Since AMPA receptor currents were reduced by 8-bromo-cGMP in vitro a direct or indirect reduction of AMPA receptor currents might possibly contribute to the antinociceptive effects of 8-bromo-cGMP. 8-Bromo-cGMP evoked antinociception appears to be largely independent of PKG-I, CNGs, PDE2 and PDE3. The antinociceptive effects of the PKG inhibitor suggest that a strong PKG activation may be responsible for high dose' 8-bromo-cGMP evoked hyperalgesia.

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 12 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:743081 HCAPLUS
DOCUMENT NUMBER: 138:395921
TITLE: Does the A118G Polymorphism at the μ-opioid Receptor Gene Protect against Morphine-6-Glucuronide Toxicity?

AUTHOR(S): Loetsch, Joern; Zimmermann, Michael; Darimont, Jutta; Marx, Claudia; Dudziak, Rafael; Skarke, Carsten; **Geisslinger, Gerd**
CORPORATE SOURCE: Department of Clinical Pharmacology, USA
SOURCE: Anesthesiology (**2002**), 97(4), 814-819
CODEN: ANESAV; ISSN: 0003-3022
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB BACKGROUND: Some, but not all, patients with renal dysfunction suffer from side effects after morphine administration because of accumulation of the active metabolite morphine-6-glucuronide (M6G). The current study aims to identify genetic causes that put patients at risk for, or protect them from, opioid side effects related to high plasma M6G. Candidate genetic causes are the single nucleotide polymorphism (SNP) A118G of the μ-opioid-receptor gene (OPRM1), which has recently been identified to result in decreased potency of M6G, and mutations in the MDR1-gene coding P-glycoprotein, of which morphine and M6G might be a substrate. METHODS Two men, aged 87 and 65 yr, with renal failure (creatinine clearance of 6 and 9 mL/min) received 30 mg/day oral morphine for **pain** treatment. Both patients had sufficient analgesia from morphine. However, while one patient tolerated morphine well despite high plasma M6G of 1735 nM, in the patient with M6G plasma concns. of 941 nM it caused severe sleepiness and drowsiness. Patients were genotyped for known SNPs of the OPRM1 and MDR1 genes. RESULTS The patient who tolerated morphine well despite high plasma M6G was a homozygous carrier of the mutated G118 allele of the μ-opioid-receptor gene, which has been previously related to decreased M6G potency. In contrast, the patient who suffered from side effects was "wild-type" for this mutation. No other differences were found between the OPRM1 and MDR1 genes. CONCLUSIONS The authors hypothesize that the A118G single nucleotide polymorphism of the μ-opioid-receptor is among the protective factors against M6G-related opioid toxicity. The observation encourages the search for pharmacogenetic reasons that cause interindividual variability of the clin. effects of morphine.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 13 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:639073 HCAPLUS
DOCUMENT NUMBER: 137:308756
TITLE: Release of algesic substances in human experimental muscle **pain**
AUTHOR(S): Tegeder, I.; Zimmermann, J.; Meller, S. T.; **Geisslinger, G.**
CORPORATE SOURCE: Pharmazentrum frankfurt, Klinikum der Johann Wolfgang Goethe-Universitat, Frankfurt am Main, DE-60590, Germany
SOURCE: Inflammation Research (**2002**), 51(8), 393-402
CODEN: INREFB; ISSN: 1023-3830
PUBLISHER: Birkhaeuser Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Objective: We employed the "delayed onset of muscle soreness" (DOMS) and the "hypertonic saline" muscle **pain** models in combination with muscle microdialysis to evaluate the role of potentially algesic substances (lactate, glutamate, prostaglandin E2 (PGE2), nitric oxide (NO) and substance P (SP)) in the development of human muscle **pain.** Methods: DOMS was induced by 2 sets of 50 concentric/eccentric contractions of the calf muscles 24 h before the start of microdialysis.

During microdialysis **pain** was stimulated through calf muscle contractions (dorsal and plantar flexions of the foot). Hypertonic saline was injected into the biceps muscle (5+200 μl 5.8% NaCl, 2 min interval) during dialysis. The calf (no treatment) and biceps (normal saline) of the other side was used as control. Results: Both models reliably induced muscle **pain** with similar intensities as assessed by visual analog scale. The DOMS exercise caused an increase of lactate in serum and the calf muscles of the DOMS leg. In addition, glutamate, PGE2 and substance P dialyzate concns. increased following contraction-induced **pain** stimulation (peak concns. 125±20 μM, 239±45 pg/mL and 60±11 pg/mL for glutamate, PGE2 and SP, resp.). This increase did not occur in the control leg (peak concns. 97±12 μM, 114±26 pg/mL and 46±9 pg/mL for glutamate, PGE2 and SP, resp.). Concns. of nitric oxide were lower in the DOMS than control leg, particularly during the first 4h of microdialysis. Injection of hypertonic saline into the biceps muscle caused a significant increase of dialyzate glutamate concns. (peak 50±3 μM) whereas glutamate remained constant after injection of normal saline (mean 26±1 μM). Injection of hypertonic saline had no effect on lactate, PGE2 or NO levels. Conclusion: Our data support the notion that an inflammatory reaction may be involved in muscle soreness following eccentric exercise, whereas the injection of hypertonic saline into the muscle probably directly stimulates muscle nociceptors and causes glutamate release.

REFERENCE COUNT: 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 14 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:581589 HCAPLUS
DOCUMENT NUMBER: 137:335682
TITLE: Mechanisms of **pain** in arthritis
AUTHOR(S): **Schaible, Hans-Georg**; Ebersberger, Andrea; Segond von Banchet, Gisela
CORPORATE SOURCE: Department of Physiology, Friedrich-Schiller University of Jena, Jena, D-07740, Germany
SOURCE: Annals of the New York Academy of Sciences (**2002**), 966(Neuroendocrine Immune Basis of the Rheumatic Diseases II), 343-354
CODEN: ANYAA9; ISSN: 0077-8923
PUBLISHER: New York Academy of Sciences
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Inflammation in the joint causes peripheral sensitization (increase of sensitivity of nociceptive primary afferent neurons) and central sensitization (hyperexcitability of nociceptive neurons in the central nervous system). The processes of sensitization are thought to be the basis of arthritic **pain** that appears as spontaneous **pain** (joints at rest) and hyperalgesia (augmented **pain** response on noxious stimulation and **pain** on normally nonpainful stimulation). Sensitization also facilitates efferent neuronal processes through which the nervous system influences the inflammatory process. Peripheral sensitization is produced by the action of inflammatory mediators such as bradykinin, prostaglandins, neuropeptides, and cytokines which activate corresponding receptors in proportions of nerve fibers. In addition, the expression of receptors, for example, bradykinin and neurokinin 1 receptors, is upregulated during inflammation. The development of hyperexcitability of spinal cord neurons is produced by various transmitter/receptor systems that constitute and modulate synaptic activation of the neurons. The key transmitter is glutamate that activates N-methyl-D-aspartate (NMDA) and non-NMDA receptors on spinal cord neurons. Blockade of these receptors prevents and reduces central

sensitization. Excitatory neuropeptides (substance P and calcitonin gene-related peptide) further central sensitization. Central sensitization also is facilitated by mediators that have complex actions (e.g., prostaglandin E2). Spinal PGE2 binds to receptors at presynaptic endings of primary afferent neurons (thus influencing synaptic release) and to receptors on postsynaptic spinal cord neurons. The administration of PGE2 to the spinal cord surface produces changes of responsiveness of spinal neurons similar to peripheral inflammation, and spinal indomethacin to the spinal cord attenuates development of hyperexcitability significantly.

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 15 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:222527 HCAPLUS
DOCUMENT NUMBER: 136:395199
TITLE: Drug interactions with patient-controlled analgesia
AUTHOR(S): Lotsch, Jorn; Skarke, Carsten; Tegeder, Irmgard; **Geisslinger, Gerd**
CORPORATE SOURCE: Pharmazentrum Frankfurt, Klinikum, Johann Wolfgang Goethe-Universitat, Frankfurt, Germany
SOURCE: Clinical Pharmacokinetics (**2002**), 41(1), 31-57
CODEN: CPKNDH; ISSN: 0312-5963
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Patient-controlled analgesia (PCA) has become standard procedure in the clin. treatment of **pain.** Its widespread use in patients with all kinds of diseases opens a variety of possible interactions between analgesics used for PCA and other drugs that might be administered concomitantly to the patient. Many of these drug interactions are of little clin. importance. However, some drug interactions have been reported to result in serious clin. problems. Drug interactions can either predominantly affect the pharmacokinetics or pharmacodynamics of the drug. Most important pharmacokinetic drug interactions occur at the level of drug metabolism or protein binding. Acceleration of methadone metabolism caused by cytochrome P 450 (CYP) 3A4 induction by antiretroviral drugs or rifampicin (rifampin) has caused methadone withdrawal symptoms. Lack of morphine formation from codeine as a result of CYP2D6 inhibition by quinidine results in an almost complete loss of the analgesic effects of codeine. Alterations of methadone protein binding caused by an inhibition of α1-acid glycoprotein synthesis by alkylating substances are another possibility for predominantly pharmacokinetically based drug interactions during PCA. Furthermore, inhibition of P-glycoprotein by anticancer drugs could result in altered transmembrane transport of morphine, methadone or fentanyl, although this has not been shown to be of clin. relevance. Synergistic effects of systemically administered opioids with spinally or topically delivered opioids or anesthetics have been reported frequently. The same is true for the opioid-sparing effects of coadministered non-opioid analgesics. Antidepressants, anticonvulsants or α2-adrenoreceptor agonists have also been shown to exert additive analgesic effects when administered together with an opioid. Inconsistent findings, however, are reported regarding the treatment of patients with opioid-induced nausea and sedation, since coadministration of antiemetics either increased or decreased the resp. adverse effects or revealed addnl. unwanted drug effects.

REFERENCE COUNT: 403 THERE ARE 403 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE

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L38 ANSWER 16 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:118508 HCAPLUS
DOCUMENT NUMBER: 136:307787
TITLE: Burst discharge in primary sensory neurons: Triggered by subthreshold oscillations, maintained by depolarizing afterpotentials
AUTHOR(S): Amir, Ron; **Michaelis, Martin**; Devor, Marshall
CORPORATE SOURCE: Department of Cell and Animal Biology, Institute of Life Sciences, Hebrew University of Jerusalem, Jerusalem, 91904, Israel
SOURCE: Journal of Neuroscience (**2002**), 22(3), 1187-1198
CODEN: JNRSDS; ISSN: 0270-6474
PUBLISHER: Society for Neuroscience
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Afferent discharge generated ectopically in the cell soma of dorsal root ganglion (DRG) neurons may play a role in normal sensation, and it contributes to paresthesias and **pain** after nerve trauma. This activity is critically dependent on subthreshold- old membrane potential oscillations; oscillatory sinusoids that reach threshold trigger low-frequency trains of intermittent spikes. Ectopic firing may also enter a high-frequency bursting mode, however, particularly in the event of neuropathy. Bursting greatly amplifies the overall ectopic barrage. In the present report we show that subthreshold oscillations and burst discharge occur in vivo, as they do in vitro. We then show that although the first spike in each burst is triggered by an oscillatory sinusoid, firing within bursts is maintained by brief regenerative post-spike depolarizing afterpotentials (DAPs). Numerical simulations were used to identify the cellular process underlying rebound DAPs, and hence the mechanism of the spike bursts. Finally, we show that slow ramp and hold (tonic) depolarizations of the sort that occur in DRG neurons during physiol. relevant events are capable of triggering sustained ectopic bursting, but only in cells with subthreshold oscillatory behavior. Oscillations and DAPs are an essential substrate of ectopic burst discharge. Therefore, any consideration of the ways in which cellular regulation of ion channel synthesis and trafficking implement normal sensation and, when disrupted, bring about neuropathic **pain** must take into account the effects of this regulation on oscillations and bursting.
REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 17 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:879723 HCAPLUS
DOCUMENT NUMBER: 136:145141
TITLE: Effects of selective COX-1 and -2 inhibition on formalin-evoked nociceptive behaviour and prostaglandin E2 release in the spinal cord
AUTHOR(S): Tegeder, Irmgard; Niederberger, Ellen; Vetter, Gregor; Brautigam, Lutz; **Geisslinger, Gerd**
CORPORATE SOURCE: Pharmazentrum Frankfurt, Klinikum der Johann Wolfgang Goethe-Universitat, Frankfurt am Main, 60590, Germany
SOURCE: Journal of Neurochemistry (**2001**), 79(4), 777-786
CODEN: JONRA9; ISSN: 0022-3042
PUBLISHER: Blackwell Science Ltd.

DOCUMENT TYPE: Journal
LANGUAGE: English
AB Nociception evoked prostaglandin (PG) release in the spinal cord considerably contributes to the induction of hyperalgesia and allodynia. To evaluate the relative contribution of cyclooxygenase-1 (COX-1) and COX-2 in this process we assessed the effects of the selective COX-1 inhibitor SC560 and the selective COX-2 inhibitor celecoxib on formalin-evoked nociceptive behavior and spinal PGE2 release. SC560 (10 and 20 mg/kg) significantly reduced the nociceptive response and completely abolished the formalin-evoked PGE2 raise. In contrast, celecoxib (10 and 20 mg/kg) was ineffective in both regards, i.e. the flinching behavior was largely unaltered and the formalin-induced PGE2 raise as assessed using microdialysis was only slightly, not significantly reduced. This suggests that the formalin-evoked rapid PG release was primarily caused by COX-1 and was independent of COX-2. Mean free spinal cord concns. of celecoxib during the formalin assay were 32.0±4.5 nM, thus considerably higher than the reported IC50 for COX-2 (3-7 nM). Therefore, the lack of efficacy of celecoxib is most likely not to be a result of poor tissue distribution. COX-2 mRNA and protein expression in the spinal cord were not affected by microdialysis alone but the mRNA rapidly increased following formalin injection and reached a maximum at 2 h. COX-2 protein was unaltered up to 4 h after formalin injection. The time course of COX-2 up-regulation suggests that the formalin-induced nociceptive response precedes COX-2 protein de novo synthesis and may therefore be unresponsive to COX-2 inhibition. Considering the results obtained with the formalin model it may be hypothesized that the efficacy of celecoxib in early injury evoked **pain** may be less than that of unselective NSAIDs.
REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 18 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:297674 HCAPLUS
DOCUMENT NUMBER: 135:44697
TITLE: Role of nitric oxide in zymosan induced paw inflammation and thermal hyperalgesia
AUTHOR(S): Guhring, H.; Tegeder, I.; Lotsch, J.; Pahl, A.; Werner, U.; Reeh, P. W.; Rehse, K.; Brune, K.; **Geisslinger, G.**
CORPORATE SOURCE: Institut fur Experimentelle Pharmakologie and Toxikologie, Universitat Erlangen-Nurnberg, Erlangen, 91054, Germany
SOURCE: Inflammation Research (**2001**), 50(2), 83-88
CODEN: INREFB; ISSN: 1023-3830
PUBLISHER: Birkhaeuser Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Objective: To assess the involvement of spinal inducible nitric oxide synthase (iNOS) in inflammation and nociception. Materials and Methods: The time course of iNOS mRNA expression in rat spinal cord and inflamed paw was assessed by means of quant. real time RT-PCR. In addition, the effects of the iNOS inhibitor L-NIL on inflammatory paw edema and thermal hyperalgesia were studied in comparison to those of the NO-donor RE-2047. L-NIL (3, 9, 27 and 81 mg/kg) and RE-2047 (3, 9 and 27 mg/kg) or vehicle were administered orally 15 min prior to the intraplantar injection of 0.625 mg zymosan. Results: Following zymosan injection, mRNA expression of iNOS increased in the inflamed paw and spinal cord with a maximum at 2.5 and 4 h, resp. In the spinal cord iNOS mRNA started to decline at 10h whereas it remained at maximum in the inflamed paw up to the end of the observation period of 24 h. As expected, RE-2047 had significant

pronociceptive and proinflammatory effects. L-NIL significantly reduced paw inflammation at 27 and 81 mg/kg but failed to reduce hyperalgesia at the doses tested. Conclusions: The results show that iNOS is upregulated in the inflamed tissue and spinal cord with a similar time course. The effects obtained with L-NIL suggest that iNOS differently contributes to the inflammatory and nociceptive response induced by zymosan.

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 19 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:293286 HCAPLUS
DOCUMENT NUMBER: 136:181786
TITLE: Release of glutamate, nitric oxide and prostaglandin E2 and metabolic activity in the spinal cord of rats following peripheral nociceptive stimulation
AUTHOR(S): Vetter, G.; **Geisslinger, G.**; Tegeder, I.
CORPORATE SOURCE: Pharmazentrum Frankfurt, Klinikum der Johann Wolfgang Goethe-Universitat, Frankfurt am Main, 60590, Germany
SOURCE: Pain (**2001**), 92(1-2), 213-218
CODEN: PAINDB; ISSN: 0304-3959
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Peripheral tissue injury and inflammation may result in a facilitated spinal nociceptive transmission and central sensitization. Particularly, nitric oxide (NO) and prostaglandins (PGs) have been shown to be key mediators involved in the induction and maintenance of this state. By means of spinal cord microdialysis we have determined interstitial glutamate, NO (NO2-/NO3-), PGE2, glycerol, glucose and lactate concns. in the dorsal horns of the spinal cord following peripheral nociceptive stimulation to gain further insight into the link between excitatory neurotransmitters and metabolic functions in the spinal cord during nociception. Formalin and zymosan injection into one hind paw evoked a biphasic release of glutamate and NO with the glutamate peaks preceding those of NO. Moreover, zymosan induced a biphasic increase of interstitial glycerol concns. accompanied by an increase of interstitial lactate indicating metabolic disturbances. In contrast, formalin injection led to an elevation of dialyzate glucose concns. which may be interpreted as an indication of enhanced metabolic activity. The sequential release of glutamate and NO in the dorsal horns of the spinal cord in response to peripheral nociceptive stimulation supports the theory that NO may act as a retrograde transmitter. The metabolic changes observed after formalin and zymosan injection suggest that an intense peripheral nociceptive stimulation may not only activate but also disturb metabolic activity and possibly membrane integrity in the spinal cord.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 20 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:219546 HCAPLUS
DOCUMENT NUMBER: 135:132488
TITLE: Prostaglandins and cyclooxygenases in the spinal cord
AUTHOR(S): Vanegas, H.; **Schaible, H.-G.**
CORPORATE SOURCE: Instituto Venezolano de Investigaciones Cientificas (IVIC), Caracas, 1020A, Venez.
SOURCE: Progress in Neurobiology (Oxford, United Kingdom) (**2001**), 64(4), 327-363
CODEN: PGNBA5; ISSN: 0301-0082
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review with 178 refs. The spinal cord is one of the sites where non-steroidal anti-inflammatory drugs (NSAIDs) act to produce analgesia and antinociception. Expression of cyclooxygenase(COX)-1 and COX-2 in the spinal cord and primary afferents suggests that NSAIDs act here by inhibiting the synthesis of prostaglandins (PGs). Basal release of PGD2, PGE2, PGF2α and PGI2 occurs in the spinal cord and dorsal root ganglia. Prostaglandins then bind to G-protein-coupled receptors located in intrinsic spinal neurons (receptor types DP and EP2) and primary afferent neurons (EP1, EP3, EP4 and IP). Acute and chronic peripheral inflammation, interleukins and spinal cord injury increase the expression of COX-2 and release of PGE2 and PGI2. By activating the cAMP and protein kinase A pathway, PGs enhance tetrodotoxin-resistant sodium currents, inhibit voltage-dependent potassium currents and increase voltage-dependent calcium inflow in nociceptive afferents. This decreases firing threshold, increases firing rate and induces release of excitatory amino acids, substance P, calcitonin gene-related peptide (CGRP) and nitric oxide. Conversely, glutamate, substance P and CGRP increase PG release. Prostaglandins also facilitate membrane currents and release of substance P and CGRP induced by low pH, bradykinin and capsaicin. All this should enhance elicitation and synaptic transfer of **pain** signals in the spinal cord. Direct administration of PGs to the spinal cord causes hyperalgesia and allodynia, and some studies have shown an association between induction of COX-2, increased PG release and enhanced nociception. NSAIDs diminish both basal and enhanced PG release in the spinal cord. Correspondingly, spinal application of NSAIDs generally diminishes neuronal and behavioral responses to acute nociceptive stimulation, and always attenuates behavioral responses to persistent nociception. Spinal application of specific COX-2 inhibitors sometimes diminishes behavioral responses to persistent nociception.

REFERENCE COUNT: 178 THERE ARE 178 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 21 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2001:81442 HCAPLUS

DOCUMENT NUMBER: 134:203018

TITLE: Effect of brain-derived neurotrophic factor on the release of substance P from rat spinal cord

AUTHOR(S): Meyer-Tuve, Annegret; Malcangio, Marzia; Ebersberger, Andrea; Mazario, Javier; **Schaible, Hans-Georg**

CORPORATE SOURCE: Institut fur Physiologie, Universitat Jena, Jena, D-07740, Germany

SOURCE: NeuroReport (**2001**), 12(1), 21-24
CODEN: NERPEZ; ISSN: 0959-4965

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Brain-derived neurotrophic factor (BDNF) can produce hyperalgesia in the adult rat. Here we assessed whether changes in the spinal release of the nociceptive peptide substance P (SP) contributes to this effect. Antibody-coated microprobes revealed a significant basal release of SP in the dorsal horn in vivo that was increased following acute knee inflammation. Microinjection of BDNF into the gray matter (0.5 μL, 10-5 M) altered SP release neither in rats with normal knees nor in rats with inflamed knee joints. In the lumbar dorsal horn slice preparation in vitro, superfusion with BDNF (100 ng/mL) could reduce SP release evoked by elec. dorsal root stimulation without modifying SP basal outflow. It is unlikely, therefore, that enhanced spinal SP release mediates the hyperalgesic effect of BDNF.

REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 22 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:603073 HCAPLUS
DOCUMENT NUMBER: 134:129694
TITLE: Monoarticular antigen-induced arthritis leads to pronounced bilateral upregulation of the expression of neurokinin 1 and bradykinin 2 receptors in dorsal root ganglion neurons of rats
AUTHOR(S): Segond von Banchet, Gisela; Petrow, Peter K.; Brauer, Rolf; **Schaible, Hans-Georg**
CORPORATE SOURCE: University of Jena, Jena, Germany
SOURCE: Arthritis Research [online computer file] (**2000**), 2(5), 424-427
CODEN: ARESFU; ISSN: 1465-9913
URL: http://arthritis-research.com/PDF/ar-2-5-424.pdf
PUBLISHER: Current Science Ltd.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB This study describes the upregulation of neurokinin 1 and bradykinin 2 receptors in dorsal root ganglion (DRG) neurons in the course of antigen-induced arthritis (AIA) in the rat knee. In the acute phase of AIA, which was characterized by pronounced hyperalgesia, there was a substantial bilateral increase in the proportion of lumbar DRG neurons that express neurokinin 1 receptors (activated by substance P) and bradykinin 2 receptors. In the chronic phase the upregulation of bradykinin 2 receptors persisted on the side of inflammation. The increase in the receptor expression is relevant for the generation of acute and chronic inflammatory **pain.**
REFERENCE COUNT: 87 THERE ARE 87 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 23 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:575164 HCAPLUS
DOCUMENT NUMBER: 134:36775
TITLE: Plasma levels after peroral and topical ibuprofen and effects upon low pH-induced cutaneous and muscle **pain**
AUTHOR(S): Steen, Astrid E.; Reeh, Peter W.; **Geisslinger, Gerd**; Steen, Kay H.
CORPORATE SOURCE: Klinik und Poliklinik fur Dermatologie der Universitat Bonn, Bonn, D-53105, Germany
SOURCE: European Journal of Pain (London) (**2000**), 4(2), 195-209
CODEN: EJPAFJ; ISSN: 1090-3801
PUBLISHER: W. B. Saunders Co. Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cutaneous applications are gaining popularity in the treatment of cutaneous **pain** and of painful disorders in joints and muscle. The low pH-**pain** model in human skin has previously been able to demonstrate the effects of NSAIDs in dose-dependent manner and to establish time-effect relationships. We examined the analgesic action of ibuprofen after cutaneous application and compared the effects with oral administration. The two studies (with n = 12 subjects each) were performed in a double-blind, randomized fashion with a 1-wk cross-over interval. In study 1 volunteers received intradermal infusions with phosphate buffered saline solution of pH 5.2 and received either 800 mg ibuprofen per os and topical placebo, or 4 g of a 5% com. ibuprofen gel

topically applied and oral placebo capsules, resp. In study 2 the same protocol was applied with painful i.m. infusion of stronger, isotonic phosphate buffer (pH 5.2). The flow rate of the pH-infusion was individually adjusted to induce **pain** with a magnitude of 20% on a visual analog scale (ranging from 'no' (0%) to 'unbearable **pain** ' (100%)). Ibuprofen (S-, R-) plasma levels after oral administrations were measured with HPLC, and after topical applications, by gas chromatog. combined with mass spectroscopy to determine plasma levels in the range of ng/mL. In the cutaneous model **pain** ratings decreased to zero after topical verum gel within 45 min of the observation period of 55 min. **Pain** reduction after peroral ibuprofen was of the same magnitude, but was achieved within only 30 min. In the muscle model, the com. ibuprofen gel did not reduce the **pain** in the acidic muscle. The peroral ibuprofen was less effective in the muscle compared to the skin **pain** model, although there was a significant progressive **pain** reduction within 55 min. Reasons for the differential susceptibility of cutaneous vs muscular acidosis **pain** to ibuprofen remain to be established.

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 24 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:531276 HCAPLUS
DOCUMENT NUMBER: 133:233218
TITLE: Regulation and immunohistochemical localization of nitric oxide synthases and soluble guanylyl cyclase in mouse spinal cord following nociceptive stimulation
AUTHOR(S): Maihofner, C.; Euchenhofer, C.; Tegeder, I.; Beck, K. F.; Pfeilschifter, J.; **Geisslinger, G.**
CORPORATE SOURCE: Universitatsstrasse 22, Institut fur Experimentelle Pharmakologie and Toxikologie, Universitat Erlangen, Erlangen, 91054, Germany
SOURCE: Neuroscience Letters (**2000**), 290(1), 71-75
CODEN: NELED5; ISSN: 0304-3940
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The localization and regulation of neuronal nitric oxide synthase (nNOS), inducible nitric oxide synthase (iNOS) and soluble guanylyl cyclase (sGC) were assessed in the spinal cord of mice stimulated by an intraplantar injection of zymosan. Both, nNOS and iNOS were upregulated in the dorsal horns of the spinal cord in response to the zymosan challenge. While nNOS was found in neurons of superficial laminae iNOS occurred in astrocytes. Thus, astrocytes might be involved in the processing of nociceptive stimuli. Expression of sGC was not affected by zymosan treatment. It was found exclusively in nerve fibers suggesting that it was predominantly localized to the presynaptic neuron. This supports the hypothesis that nitric oxide (NO) acts as retrograde messenger in spinal nociceptive processing.

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 25 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:526123 HCAPLUS
DOCUMENT NUMBER: 133:233123
TITLE: Differential effects of calcitonin gene-related peptide and calcitonin gene-related peptide 8-37 upon responses to N-methyl-d-aspartate or (R,S)-α-amino-3-hydroxy-5-methylisoxazole-4-propionate in spinal nociceptive neurons with knee

joint input in the rat

AUTHOR(S): Ebersberger, A.; Charbel Issa, P.; Vanegas, H.; **Schaible, H.-G.**

CORPORATE SOURCE: Teichgraben 8, Institut fur Physiologie, Friedrich-Schiller-Universitat, Jena, 07740, Germany

SOURCE: Neuroscience (Oxford) (**2000**), 99(1), 171-178
CODEN: NRSCDN; ISSN: 0306-4522

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Calcitonin gene-related peptide is involved in the spinal processing of nociceptive input from the knee joint and in the generation and maintenance of joint inflammation-evoked hyperexcitability of spinal cord neurons. The present study examined whether this peptide influences the excitation of nociceptive spinal cord neurons by agonists at the N-methyl-d-aspartate and the non-N-methyl-d-aspartate [(R,S)-α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA)/kainate] receptors, both of which are essential for the excitation and hyperexcitability of spinal cord neurons. In anesthetized rats extracellular recordings were made from dorsal horn neurons with knee input, and compds. were administered ionophoretically close to the neurons recorded. When calcitonin gene-related peptide was administered the responses of the neurons to the application of both N-methyl-d-aspartate and AMPA were increased. The coadministration of the antagonist calcitonin gene-related peptide 8-37 had no effect on the responses to N-methyl-d-aspartate, but it prevented the enhancement of the responses to N-methyl-d-aspartate by calcitonin gene-related peptide. By contrast, the administration of calcitonin gene-related peptide 8-37 enhanced the responses of the neurons to AMPA, and it did not antagonize but rather increased the effects of calcitonin gene-related peptide on these responses. The data suggest that the facilitatory role of calcitonin gene-related peptide on the development and maintenance of inflammation-evoked hyperexcitability is caused at least in part by the modulation of the activation of the dorsal horn neurons through their N-methyl-d-aspartate and non-N-methyl-d-aspartate receptors. The different effects of calcitonin gene-related peptide 8-37 on the responses to N-methyl-d-aspartate and AMPA suggest that different intracellular pathways may facilitate the activation of N-methyl-d-aspartate and ionotropic non-N-methyl-d-aspartate receptors.

REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 26 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2000:299463 HCAPLUS

DOCUMENT NUMBER: 132:303409

TITLE: Postoperative **pain** control following remifentanil-based anesthesia for major abdominal surgery

AUTHOR(S): Albrecht, S.; Fechner, J.; **Geisslinger, G.**; Maass, A. B.; Upadhyaya, B.; Moecke, H. -P.; Haigh, C.; Schuttler, J.

CORPORATE SOURCE: Klinik fur Anaesthesiologie, University of Erlangen-Nuremberg, Erlangen, D-91054, Germany

SOURCE: Anaesthesia (**2000**), 55(4), 315-322
CODEN: ANASAB; ISSN: 0003-2409

PUBLISHER: Blackwell Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Eighty patients undergoing major abdominal surgery using remifentanil-based anesthesia were randomly allocated in a double-blind manner to receive an i.v. bolus of fentanyl, buprenorphine, morphine or

piritramide 20 min before the end of surgery. A reduced dose was administered postoperatively when patients reported moderate **pain** . Subsequent analgesia was provided by patient-controlled analgesia (PCA). The mean time from the end of anesthesia to spontaneous respiration was 9±5 min. At first **pain** assessment, 63% of patients reported no or mild **pain**; 80% of patients required the second opioid bolus, those receiving piritramide needed the bolus significantly later than patients receiving buprenorphine or fentanyl. First PCA requirement also occurred significantly later in the piritramide group. This technique provided effective postoperative **pain** relief and transition to routine PCA and did not compromise recovery.

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 27 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:154951 HCAPLUS
DOCUMENT NUMBER: 132:288283
TITLE: Population pharmacokinetics of fast release oral diclofenac in healthy volunteers: relation to pharmacodynamics in an experimental **pain** model
AUTHOR(S): Lotsch, Jorn; Kettenmann, Birgit; Renner, Bertold; Drover, David; Brune, Kay; **Geisslinger, Gerd** ; Kobal, Gerd
CORPORATE SOURCE: Department of Anesthesia, Stanford University School of Medicine, Stanford, CA, 94305-5640, USA
SOURCE: Pharmaceutical Research (**2000**), 17(1), 77-84
CODEN: PHREEB; ISSN: 0724-8741
PUBLISHER: Kluwer Academic/Plenum Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Population pharmacokinetics of a fast release diclofenac were assessed with special focus on pharmacodynamic implications. In a double blind four-way crossover study, 20 healthy volunteers received orally 50 and 100 mg diclofenac-Na effervescent ("fast-release NSAID"), 50 mg diclofenac tablets ("control"), or placebo. Population pharmacokinetics of the fast release diclofenac were assessed using a nonlinear mixed effects modeling approach (NONMEM). Analgestic effects were investigated by means of an exptl. **pain** model based on both **pain**-ratings and cortical evoked potentials after specific stimulation of nasal nociceptors with short pulses of gaseous CO2. Pharmacokinetics of fast release diclofenac were best described by a two-compartment population model, with an estimated terminal half-life 1.2 h. Pharmacokinetics of diclofenac tablets were highly variable and a population pharmacokinetic model could not be obtained. As an indication of an early onset of analgesic effects, 100 mg fast release diclofenac but not the tablets significantly reduced the amplitudes of **pain**-related evoked potentials at 30 min after administration. Earlier drug absorption and lower pharmacokinetic variability of the fast-release formulation are likely to be preserved in a population.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 28 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:127145 HCAPLUS
DOCUMENT NUMBER: 133:68196
TITLE: Effects of antagonists to high-threshold calcium channels upon spinal mechanisms of **pain**, hyperalgesia and allodynia
AUTHOR(S): Vanegas, H.; **Schaible, H.-G.**

CORPORATE SOURCE: Instituto Venezolano de Investigaciones Cientificas (IVIC), Caracas, Venez.
SOURCE: Pain (2000), 85(1-2), 9-18
CODEN: PAINDB; ISSN: 0304-3959
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with .apprx.70 refs. High-threshold voltage-dependent calcium channels enable calcium ions to enter neurons upon depolarization and thereby influence synaptic mediator/receptor systems, membrane excitability levels, second and third messenger concentration, and gene expression. These phenomena underlie several processes including those of normal nociception and of hyperalgesia and allodynia. The present article deals with the role of spinal L-, N- and P/Q-type calcium channels in short-lasting nociception as well as in the hyperalgesia and allodynia elicited by chemical irritants of peripheral nociceptors, inflammatory and mech. lesions of peripheral tissues, and lesions of peripheral nerves. The studies summarized herein are based on the spinal delivery of specific antagonists to high-threshold calcium channels, and reveal that blockade of L-type, P/Q-type and, particularly, N-type channels can prevent, attenuate, or both, subjective **pain** as well as primary and/or secondary hyperalgesia and allodynia in a variety of exptl. and clin. conditions.

REFERENCE COUNT: 75 THERE ARE 75 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 29 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:623022 HCAPLUS
TITLE: Membrane potential oscillations in dorsal root ganglion neurons: role in normal electrogenesis and neuropathic **pain**
AUTHOR(S): Amir, Ron; **Michaelis, Martin**; Devor, Marshall
CORPORATE SOURCE: Department of Cell and Animal Biology, Institute of Life Sciences, Hebrew University of Jerusalem, Jerusalem, 91904, Israel
SOURCE: Journal of Neuroscience (**1999**), 19(19), 8589-8596
CODEN: JNRSDS; ISSN: 0270-6474
PUBLISHER: Society for Neuroscience
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Abnormal afferent discharge originating at ectopic sites in injured primary sensory neurons is thought to be an important generator of paraesthesias, dysaesthesias, and chronic neuropathic **pain.** We report here that the ability of these neurons to sustain repetitive discharge depends on intrinsic resonant properties of the cell membrane and that the prevalence of this characteristic increases after nerve injury. Recording from primary sensory neurons in excised rat dorsal root ganglia, we found that some cells show subthreshold oscillations in their membrane potential. The amplitude, frequency, and coherence of these oscillations were voltage sensitive. Oscillations gave rise to action potentials when they reached threshold. Indeed, the presence of oscillations proved to be a necessary condition for sustained spiking both at resting membrane potential and on depolarization; neurons without them were incapable of sustained discharge even on deep depolarization. Previous nerve injury increased the proportion of neurons sampled that had subthreshold oscillations, and hence the proportion that generated ectopic spike discharge. Oscillatory behavior and ectopic spiking were eliminated by [Na+]o substitution or bath application of lidocaine or tetrodotoxin

(TTX), under conditions that preserved axonal spike propagation. This suggests that a TTX-sensitive Na+ conductance contributes to the oscillations. Selective pharmacol. suppression of subthreshold oscillations may offer a means of controlling neuropathic paraesthesias and **pain** without blocking afferent nerve conduction.

REFERENCE COUNT: 62 THERE ARE 62 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 30 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:581466 HCAPLUS
TITLE: Distribution of sensory properties among axotomized cutaneous C-fibres in adult rats
AUTHOR(S): **Michaelis, M.**; Blenk, K.-H.; Vogel, C.; Janig, W.
CORPORATE SOURCE: Physiologisches Institut, Christian-Albrechts-Universitat, Kiel, 24098, Germany
SOURCE: Neuroscience (Oxford) (**1999**), 94(1), 7-10
CODEN: NRSCDN; ISSN: 0306-4522
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A few hours after peripheral axons of cutaneous afferent neurons have been transected, some of their novel endings become excitable by phys. or chemical stimuli.1,7,8,12-14 It has been assumed that these axon endings preferentially respond to those stimuli which have excited their previous receptive endings. We studied the prevalence of sensory properties among 784 unmyelinated sural nerve fibers which had been axotomized 2-24 h before, by applying mech. and thermal forces to the nerve lesion site. Among 126 responding C-fibers, the majority was unimodal, responding exclusively to mech. (31%), cold (23%) or heat (18%) stimuli. The remainder were either mechano-heat sensitive (10%), mechano-cold sensitive (6%) or heat and cold sensitive (12%). The distribution of sensory properties among acutely axotomized sural nerve C-fibers is therefore largely similar to the recently published distribution of receptor types among intact sural nerve C-fiber afferents.11 Thus, the hypothesis that responses of axotomized afferent fibers reflect their original receptive properties is corroborated. Knowledge of underlying transduction mechanisms may lead to specific pharmacol. tools for suppression of ectopic discharges in unmyelinated axotomized afferents, which probably contribute to neuropathic **pain** states.

REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 31 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:293980 HCAPLUS
DOCUMENT NUMBER: 131:110854
TITLE: Application of microdialysis for the determination of muscle and subcutaneous tissue concentrations after oral and topical ibuprofen administration
AUTHOR(S): Tegeder, Irmgard; Muth-Selbach, Uta; Lotsch, Jorn; Rusing, Guido; Oelkers, Rieke; Brune, Kay; Meller, Steve; Kelm, Garry R.; Sorgel, Fritz; **Geisslinger, Gerd**
CORPORATE SOURCE: Department of Experimental and Clinical Pharmacology and Toxicology, University Erlangen/Nurnberg, Erlangen, Germany
SOURCE: Clinical Pharmacology & Therapeutics (St. Louis) (**1999**), 65(4), 357-368
CODEN: CLPTAT; ISSN: 0009-9236
PUBLISHER: Mosby, Inc.

DOCUMENT TYPE: Journal
LANGUAGE: English
AB The topical administration of non-steroidal antiinflammatory drugs (NSAIDs) is widely used for the treatment of soft tissue **pain.** However, it is not known whether effective tissue concns. are reached with the topical route. To evaluate and compare unbound muscle and s.c. tissue ibuprofen concns. with use of microdialysis after topical and oral administration. In a 2-way crossover design, 11 healthy volunteers received either 800 mg oral ibuprofen or 16 g of 5% ibuprofen gel applied onto the skin of the thigh (defined area, 17 + 19 cm). Microdialysis catheters were inserted into the medial vastus muscle (25 to 30 mm) and into the s.c. adipose layer of the thigh (4 to 5 mm). Dialyzate was collected in 20-min intervals up to 5 h. Essentially all of the orally administered dose was recovered in urine as ibuprofen or metabolites during 24 h, but only about 0.55% of the topically administered dose was recovered. The relative systemic bioavailability of ibuprofen gel, based on urine recovery data, was (mean ± SD) 0.57% ± 0.30%. Mean values of the dialyzate areas under the drug concentration-time curves after topical and oral administration were 731.2 ± 605.0 and 176.6 ± 122.9 ng • h • mL-1 for s.c. tissue and 63.5 ± 90.3 and 213.4 ± 117.2 ng • h • mL-1 for muscle, resp. Muscle dialyzate concns. after topical administration varied considerably among the subjects. These results suggest that, if target tissue concns. correlate directly with the degree of **pain** relief, patients with **pain** caused by dermal or s.c. tissue damage will have greater **pain** relief after topical administration of ibuprofen accompanied with less systemic side effects. In addition, a proportion of patients with muscle **pain** may also experience **pain** relief from topical ibuprofen.
REFERENCE COUNT: 76 THERE ARE 76 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 32 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:60394 HCAPLUS
DOCUMENT NUMBER: 130:306425
TITLE: Peripheral antihyperalgesic effect of morphine to heat, but not mechanical, stimulation in healthy volunteers after ultraviolet-B irradiation
AUTHOR(S): Koppert, Wolfgang; Likar, Rudolf; **Geisslinger, Gerd**; Zeck, Susanne; Schmelz, Martin; Sittl, Reinhard
CORPORATE SOURCE: Department of Anesthesiology, University of Erlangen-Nuremberg, Erlangen, D-91054, Germany
SOURCE: Anesthesia & Analgesia (Baltimore) (**1999**), 88(1), 117-122
CODEN: AACRAT; ISSN: 0003-2999
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The objective of this study was to evaluate direct peripheral analgesic effects of morphine using a peripheral model of hyperalgesia and the technique of IV regional anesthesia (IVRA), thus allowing the differentiation between central and peripheral mechanisms of action. Two spots on the ventral sides of both forearms in 12 volunteers were irradiated with UVB to induce thermal and mech. hyperalgesia. One day after the induction of the inflammatory reaction, 40 mL of morphine hydrochloride 0.01% was administered via IVRA. Calibrated heat and phasic mech. stimuli were applied to differentially determine impairments of tactile and nociceptive perception. Touch and phasic mech. stimuli of noxious intensity to normal skin did not reveal altered responsiveness caused by

morphine. In contrast, the administration of morphine significantly increased heat **pain** thresholds in the UV-B-pretreated skin areas. The peripheral antihyperalgesic effects of morphine were demonstrated only in inflamed skin areas. Direct central analgesic effects were ruled out by the lack of measurable plasma concns. of morphine and its metabolites. Morphine 0.01% significantly diminished thermal, but not mech., hyperalgesia by a peripheral mode of action, which suggests inhibition of effector pathways leading to heat, but not mech., sensitization. The peripheral analgesic effects of morphine were studied using modified IV regional anesthesia. When administered 1 day after the induction of dermal inflammation, morphine 0.01% diminished heat, but not primary mech., hyperalgesia. Therefore, suppression of mech. hyperalgesia seen in previous studies could be predominantly due to inhibition of secondary (central) mech. hyperalgesia.

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 33 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1998:708935 HCAPLUS
DOCUMENT NUMBER: 129:326090
TITLE: Ibuprofen thio esters as inhibitors of Nf-κB-dependent **pain** and inflammation mediator formation
INVENTOR(S): Bang, Holger; Brune, Kay; **Geisslinger, Gerd**; Pahl, Andreas; Scheuren, Nicole; Neupert, Werner
PATENT ASSIGNEE(S): Paz Arzneimittel-Entwicklungsgesellschaft m.b.H., Germany
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9847502	A1	19981029	WO 1998-EP2318	19980420 <--
W: CA, JP, RU, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
DE 19716713	A1	19981022	DE 1997-19716713	19970421 <--
CA 2287501	AA	19981029	CA 1998-2287501	19980420 <--
EP 977560	A1	20000209	EP 1998-921471	19980420 <--
EP 977560	B1	20040630		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
JP 2001521539	T2	20011106	JP 1998-545011	19980420 <--
RU 2204388	C2	20030520	RU 1999-124628	19980420 <--
AT 270100	E	20040715	AT 1998-921471	19980420
PT 977560	T	20041029	PT 1998-921471	19980420
ES 2219889	T3	20041201	ES 1998-921471	19980420

PRIORITY APPLN. INFO.: DE 1997-19716713 A 19970421
WO 1998-EP2318 W 19980420

AB Medicaments containing CoA thio esters of arylpropionic acids, arylacetic acids, acetylsalicylates, R-ibuprofen, ibuprofen racemates with ≤49% S-ibuprofen, or derivs. of these compds. which are metabolized in an analogous manner are used to treat acute and/or chronic **pain**, all types of inflammation, and other symptoms of inflammatory processes. These agents selectively block the activation of transcription factor Nf-κB by inflammatory stimuli and thereby interfere with the development of inflammatory symptoms and **pain.** Thus,

R-ibuprofen CoA thioester (1-100 μM) dose-dependently inhibited the activation of Nf-κB in phorbol ester-stimulated Jurkat cells in vitro.

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 34 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:620091 HCAPLUS
DOCUMENT NUMBER: 129:314579
TITLE: Inflammatory mediators sensitize acutely axotomized nerve fibers to mechanical stimulation in the rat
AUTHOR(S): **Michaelis, Martin**; Vogel, Carola; Blenk, Karl-Heinz; Arnarson, Adalsteinn; Janig, Wilfrid
CORPORATE SOURCE: Physiologisches Institut, Christian-Albrechts-Universitat, Kiel, 24098, Germany
SOURCE: Journal of Neuroscience (**1998**), 18(18), 7581-7587
CODEN: JNRSDS; ISSN: 0270-6474
PUBLISHER: Society for Neuroscience
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Many axotomized myelinated as well as unmyelinated cutaneous nerve fibers are sensitive to mech. stimuli applied to the cut nerve end within a few hours after nerve lesion. Here we investigated the influence of inflammatory mediators on this ectopic mechanosensitivity after cutting and ligating the sural nerve in anesthetized rats. Neural activity was recorded from single axons in filaments teased from the sural or sciatic nerve proximally to the lesion site 2-33 h after axotomy. Using calibrated von Frey hairs (1.0-128.5 mN), 30 s trains of phasic stimuli were applied to the cut nerve end immediately before and after local application of a mixture of inflammatory mediators [inflammatory soup (IS), consisting of bradykinin, 5-HT, prostaglandin E2, histamine (all 10 μM), and K+ 7 mM, pH 7.0] for 2 min. Before as well as after IS application, von Frey thresholds were significantly lower in myelinated (A) fibers than in unmyelinated (C) fibers. IS application enhanced the ectopic mech. excitability, as expressed in reduced von Frey thresholds and increased response magnitudes, of most severed mechanosensitive C fibers (77%) and some mechanosensitive A fibers (46%). The sensitization lasted for 10-40 min after a 2 min IS application. Addnl., among axotomized nerve fibers unresponsive to probing of the nerve lesion site before IS application, 1 of 63 (1.6%) A and 3 of 106 (2.8%) C fibers became mechanosensitive immediately after IS application. The results indicate that after axotomy, inflammatory processes augment touch-evoked ectopic activity in lesioned sensory nerve fibers. Because many affected afferents are presumably of nociceptive function, their enhanced neural barrage may contribute to neuropathic **pain** states.
REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 35 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:6671 HCAPLUS
DOCUMENT NUMBER: 128:84292
TITLE: Lack of analgesic activity of morphine-6-glucuronide after short-term intravenous administration in healthy volunteers
AUTHOR(S): Lotsch, Jorn; Kobal, Gerd; Stockmann, Anne; Brune, Kay; **Geisslinger, Gerd**
CORPORATE SOURCE: Department of Experimental and Clinical Phar- macology and Toxlcology, University of Erlangen-Nurnberg, Erlangen, Germany

SOURCE: Anesthesiology (**1997**), 87(6), 1348-1358
CODEN: ANESAV; ISSN: 0003-3022
PUBLISHER: Lippincott-Raven Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The analgesic activity of morphine-6-glucuronide (M-6-G) is well recognized for its contribution to the effects of morphine and its possible use as an opioid analgesic with a wider therapeutic range than morphine. The present study attempted to quantify the relative contribution of M-6-G to analgesia observed after systemic administration of morphine. In a placebo-controlled, sixfold crossover study in 20 healthy men, the effects of M-6-G were assessed at steady-state plasma concns. of M-6-G identical to and two and three times higher than those measured after administration of morphine. Morphine and M-6-G were administered as an i.v. bolus followed by infusion over 4 h. Dosage A was M-6-G-bolus of 0.015 mg/kg plus infusion of 0.0072 mg/kg-1/h-1. Dosage B was M-6-G-bolus of 0.029 mg/kg plus infusion of 0.014 mg/kg-1/h-1. Dosage C was M-6-G-bolus of 0.044 mg/kg plus infusion of 0.022 mg kg-1/h-1. Dosage D was a morphine bolus of 0.14 mg/kg plus infusion of 0.05 mg/kg-1/h-1 for 4 h. Dosage E was M-6-G combined with morphine (doses A + D). Dosage F was a placebo. The analgesic effects of M-6-G and morphine were measured before administration of the bolus and after 3.5 h using an exptl. **pain** model based on **pain**-related cortical potentials and **pain** ratings after specific stimulation of the nasal nociceptor with short pulses of gaseous carbon dioxide. Morphine significantly reduced subjective and objective **pain** correlates compared with placebo. In contrast, M-6-G produced no statistically significant effects. The addition of M-6-G to morphine did not increase the effects of morphine. Morphine produced significantly more side effects than M-6-G. After short-term i.v. administration at doses that produce plasma concns. of M-6-G similar to those seen after administration of morphine, M-6-G had no analgesic effects in the present placebo-controlled study in healthy volunteers.

REFERENCE COUNT: 70 THERE ARE 70 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 36 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1997:573837 HCAPLUS
DOCUMENT NUMBER: 127:261222

TITLE: Algesics excite axotomized afferent nerve fibers within the first hours following nerve transection in rats

AUTHOR(S): **Michaelis, Martin**; Vogel, Carola; Blenk, Karl-Heinz; Jaenig, Wilfrid
CORPORATE SOURCE: Physiologisches Institut, Christian-Albrechts-Universitaet, Olshausenstr. 40, D-24098, Kiel, Germany

SOURCE: Pain (**1997**), 72(3), 347-354
CODEN: PAINDB; ISSN: 0304-3959
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The direct consequences of a peripheral nerve injury at the lesion site itself are often twofold: axons of afferent (and efferent) nerve fibers are transected and the tissue surrounding the nerve injury site is inflamed. Recent studies have shown that a few hours after nerve transection, axotomized myelinated (A) and unmyelinated (C) afferents may respond to mech. and thermal stimuli applied to the cut nerve end. Here, 5-24 h after sural nerve ligation and transection we studied the ectopic excitability of axotomized cutaneous A and C fibers by chemical agents, most of which excite afferent terminals in skin. Topical application of

bradykinin (BK; 10-4 M) to the nerve stump excited 7.3% of all C fibers tested. Application of prostaglandin E2 (PGE2), a solution with increased proton concentration (pH 6.0) or a combination of inflammatory mediators ('inflammatory soup', containing histamine, 5-HT, BK and PGE2 (all 10-5 M) at a pH of 7.0) activated 2.7-4.3% of all C fibers tested. Hypertonic saline solution (HS; 4.5%) and capsaicin, painful irritants, excited 8.3% and 5.0% of the C fibers, resp. Among the axotomized A fibers tested, between 0.8% and 1.7% were excited by BK, PGE2, inflammatory soup (IS) or HS. Capsaicin and acid pH did not excite cut A fibers. In total, the number of chemical excited C fibers (50/547) significantly exceeded the number of activated A fibers (10/469). Local norepinephrine application (0.5-2.4·10-3 M) did not activate A or C fibers (234 and 224 fibers tested, resp.). The results indicate that already during the first hours after transection of a peripheral skin nerve a significant proportion of axotomized afferents can be excited by topical chemical stimulation. This evoked activity is preferentially found in unmyelinated fibers, many of which have nociceptive functions. Chemical evoked discharges as described in the present study may therefore contribute to the induction of **pain** and paraesthesias in patients with peripheral nerve lesion when the injury site is inflamed.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 37 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:509744 HCAPLUS
DOCUMENT NUMBER: 127:199525
TITLE: Pharmacokinetic-pharmacodynamic relationships for analgesics
AUTHOR(S): Suri, A.; Estes, K. S.; **Geisslinger, G.**; Derendorf, H.
CORPORATE SOURCE: College Pharmacy, University Florida, Gainesville, FL, USA
SOURCE: International Journal of Clinical Pharmacology and Therapeutics (**1997**), 35(8), 307-323
CODEN: ICTHEK; ISSN: 0946-1965
PUBLISHER: Dustri-Verlag Dr. Karl Feistle
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 142 refs. is given on pharmacokinetic(PK)-pharmacodynamic (PD) relationships for analgesics. A major goal of current **pain** research is to develop scientifically-based guidelines to optimize selection of analgesic drug doses and control **pain.** Numerous clin. studies showed that the drug dose required to effectively alleviate **pain** is often highly variable. Exptl. tools that measure analgesic response and drug disposition after administration of analgesics were used to predict the therapeutic effects of analgesics in individual patients. PK/PD modeling involves anal. of drug disposition data and drug efficacy data. Results from PK/PD anal. that successfully identify a relationship between drug dose, drug concentration, and effect were used to predict the effects of drug dose on analgesic effect in individuals. The ultimate goal is to provide patients with better **pain** relief by understanding variables that affect the analgesic concentration/effect relationship.

L38 ANSWER 38 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:344391 HCAPLUS
DOCUMENT NUMBER: 127:90300
TITLE: Comparison of the antinociception produced by two oral formulations of ibuprofen. Ibuprofen effervescent vs ibuprofen tablets

AUTHOR(S): Hummel, T.; Cramer, O.; Mohammadian, P.; **Geisslinger, G.**; Pauli, E.; Kobal, G.
CORPORATE SOURCE: Department Experimental Clinical Pharmacology Toxicology, University Erlangen-Nurnberg, Erlangen, D-91054, Germany
SOURCE: European Journal of Clinical Pharmacology (**1997**), 52(2), 107-114
CODEN: EJCPAS; ISSN: 0031-6970
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The dose-related effects of both ibuprofen tablets and ibuprofen effervescent [placebo, 400 and 800 mg ibuprofen (Aktren)] on phasic **pain** was compared. Twenty volunteers participated in this randomized, double-dummy, fivefold crossover study. Measurements were obtained before and 15, 60 and 240 min after drug administration. **Pain** was produced by CO2 pulses applied to the left nostril. Subjects rated the intensity of the painful stimuli by means of a visual analog scale. In addition, chemosomatosensory event-related potentials were recorded. Ibuprofen produced a dose-related decrease in **pain** -related potential amplitudes P1N1, indicating its antinociceptive effects. Higher plasma concns. of ibuprofen were reached 15 - 40 min after administration of the effervescent while ibuprofen tablets had a tmax 60 - 90 min after administration. In addition, 60 min after intake of the effervescent a prolongation of the latencies of the potentials was observed, possibly reflecting superior antinociceptive properties when compared to ibuprofen tablets. In addition, the effervescent appeared to have more consistent effects on intensity ests. compared to ibuprofen tablets.

L38 ANSWER 39 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:285037 HCAPLUS
DOCUMENT NUMBER: 127:3786
TITLE: Peripheral noxious stimulation releases spinal PGE2 during the first phase in the formalin assay of the rat
AUTHOR(S): Scheuren, N.; Neupert, W.; Ionac, M.; Neuhuber, W.; **Geisslinger, G.**
CORPORATE SOURCE: Dep. Experimental and Clinical Pharmacology and Toxicology, Univ. Erlangen-Nuernberg, Erlangen, D-91054, Germany
SOURCE: Life Sciences (**1997**), 60(21), PL295-PL300
CODEN: LIFSAK; ISSN: 0024-3205
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Injection of formalin (5%; 50μl) into the dorsal surface of the hind paw of rats evoked a characteristic biphasic flinching behavior of the injured paw accompanied by a significant increase in the interstitial prostaglandin E2 (PGE2) concentration of the dorsal lumber spinal cord. Interestingly, the increase in PGE2 concentration was only observed during the first phase of the formalin behavioral response (during the 0-10 and 10-20 min microdialysis-sample). Saline paw injection did not have a significant effect on behavior or on PGE2 concentration These data suggest that spinal release of PGE2 is involved in nociceptive processing in the formalin-induced hyperalgesia model of the rat during the first but not second phase.

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 40 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:209411 HCAPLUS
DOCUMENT NUMBER: 126:263056
TITLE: C-fos expression in lumbar spinal cord neurons in the polyarthritic rat: physiological and pharmacological aspects
AUTHOR(S): Abbadie, C.; Besson, J.-M.
CORPORATE SOURCE: Physiopharmacol. System Nerveux, INSERM, Paris, 75014, Fr.
SOURCE: Neuropeptides, Nociception, and Pain, Symposium, Mainz, Oct. 8-10, 1992 (**1994**), Meeting Date 1992, 403-424. Editor(s): **Hoekfelt, Tomas; Schaible, Hans-Georg; Schmidt, Robert F.** Chapman & Hall: London, UK.
CODEN: 64DPAS
DOCUMENT TYPE: Conference
LANGUAGE: English
AB Here, the authors quant. evaluated the Fos-like immunoreactivity (Fos-LI) in lumbar spinal cord neurons: (1) during the development of adjuvant-induced arthritis and in the absence of any intentional stimulation, (2) following a calibrated mech. pressure of the ankle comparatively in arthritic and healthy rats, and (3) during chronic treatment with aspirin or acetaminophen. The data on aspirin and acetaminophen are relevant to the treatment of chronic inflammatory disorders such as rheumatoid arthritis. The Fos-LI technique could be used to study the effects of various putative analgesics in chronic **pain** models.

L38 ANSWER 41 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:209410 HCAPLUS
DOCUMENT NUMBER: 126:259506
TITLE: Nociceptive stimulation induces immediate-early gene expression and increases GABA immunoreactivity in spinal neurons
AUTHOR(S): Toelle, T. R.; Castro-Lopes, J. M.; Zieglgaensberger, W.
CORPORATE SOURCE: Clinical Neuropharmacology, Max-Planck-Institute of Psychiatry, Clinical Institute, Munchen, D-80804, Germany
SOURCE: Neuropeptides, Nociception, and Pain, Symposium, Mainz, Oct. 8-10, 1992 (**1994**), Meeting Date 1992, 385-402. Editor(s): **Hoekfelt, Tomas; Schaible, Hans-Georg; Schmidt, Robert F.** Chapman & Hall: London, UK.
CODEN: 64DPAS
DOCUMENT TYPE: Conference
LANGUAGE: English
AB The authors report the expression of the immediate-early gene encoded protein c-Fos and the alteration of GABA immunoreactivity in spinal dorsal horn neurons of rats bearing unilateral chronic inflammation and the effect of several analgesic substances on the expression of c-Fos following acute noxious heat stimulation.

L38 ANSWER 42 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:209408 HCAPLUS
DOCUMENT NUMBER: 126:262719
TITLE: Changes in immediate early gene expression, neuropeptide immunoreactivity and other neuronal markers in the spinal cord and dorsal root ganglion in

a rat model of mononeuropathy
AUTHOR(S): Hunt, S.P.; Smith, G.D.; Bond, A.; Munglani, R.; Thomas, K.; Elliott, P.J.
CORPORATE SOURCE: Molecular Neurobiology Unit, MRC Centre, Cambridge, CB2 2QH, UK
SOURCE: Neuropeptides, Nociception, and Pain, Symposium, Mainz, Oct. 8-10, 1992 (**1994**), Meeting Date 1992, 329-348. Editor(s): **Hoekfelt, Tomas; Schaible, Hans-Georg; Schmidt, Robert F.** Chapman & Hall: London, UK.
CODEN: 64DPAS
DOCUMENT TYPE: Conference
LANGUAGE: English
AB This study examines changes in neuronal markers (including the immediate early-onset genes c-fos and c-jun) in the spinal cord and dorsal root ganglia of the mononeuropathic rat.

L38 ANSWER 43 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:209407 HCAPLUS
DOCUMENT NUMBER: 126:262371
TITLE: Changes in spinal NK1 receptors accompany peripheral inflammation
AUTHOR(S): Seybold, V. S.; Stucky, C. L.; Aanonsen, L. M.; Galeazza, M. T.; Abrahams, L. G.; Parsons, A. M.
CORPORATE SOURCE: Department of Cell Biology and Neuroanatomy and Graduate Program in Neuroscience, University of Minnesota, Minneapolis, MN, 554455, USA
SOURCE: Neuropeptides, Nociception, and Pain, Symposium, Mainz, Oct. 8-10, 1992 (**1994**), Meeting Date 1992, 311-328. Editor(s): **Hoekfelt, Tomas; Schaible, Hans-Georg; Schmidt, Robert F.** Chapman & Hall: London, UK.
CODEN: 64DPAS
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review with 47 refs. The authors studied the regulation of tachykinin receptors in models of chronic **pain** because of the potential involvement of substance P in modulating the excitability of spinal neurons and thus central sensitization. Substance P binds with highest affinity to the NK1 receptors (R. Quirion, 1985). Most recently, the authors have completed studies of the time course, distribution, and mechanism underlying changes in NK1 receptors in a model of peripheral inflammation in the art. Many of the changes in NK1 receptor binding paralleled those that occur in an animal model for neuropathic **pain.** The changes in NK1 receptor binding suggest that spinal neurons alter the parameters for activation of NK1 receptors in order to maintain or enhance the efficacy of substance P synaptic transmission during hyperalgesia.

L38 ANSWER 44 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:209405 HCAPLUS
DOCUMENT NUMBER: 126:262370
TITLE: Spinal cord activity during unilateral inflammation of the ankle in the rat: electrophysiological changes and importance of endogenous kappa opioids
AUTHOR(S): **Schaible, H.-G.**; Grubb, B. D.; Stiller, R. U.; Pfrommer, U.; Hanesch, U.
CORPORATE SOURCE: Physiologisches Institut, Wurzburg, 97070, Germany
SOURCE: Neuropeptides, Nociception, and Pain, Symposium, Mainz, Oct. 8-10, 1992 (**1994**), Meeting Date

1992, 285-300. Editor(s): **Hoekfelt, Tomas; Schaible, Hans-Georg; Schmidt, Robert F.** Chapman & Hall: London, UK.
CODEN: 64DPAS
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review with 47 refs. on the role of κ opioid receptors in the spinal cord during chronic unilateral inflammation in rat ankle. Topics include: the unilateral inflammation at the ankle of the rat as a model of chronic inflammatory **pain**; spinal cord activity during unilateral inflammatory at the ankle; the effects of the κ opioid antagonist nor-binaltorphamine on spinal neurons with input from the normal and inflamed ankle joint.

L38 ANSWER 45 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:209404 HCAPLUS
DOCUMENT NUMBER: 126:246864
TITLE: Exogenous versus endogenous chronic stimulation of opioidergic system: advantages and limitations in **pain** control
AUTHOR(S): Noble, F.; Fournie-Zaluski, M.-C.; Roques, B. P.
CORPORATE SOURCE: Dep. Chim. Org., Univ. Rene Descartes, Paris, 75270, Fr.
SOURCE: Neuropeptides, Nociception, and Pain, Symposium, Mainz, Oct. 8-10, 1992 (**1994**), Meeting Date 1992, 263-283. Editor(s): **Hoekfelt, Tomas; Schaible, Hans-Georg; Schmidt, Robert F.** Chapman & Hall: London, UK.
CODEN: 64DPAS
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review, with 44 refs. A recently developed series of highly selective and systemically active δ agonists such as Tyr-X-Gly-Phe-Leu-Thr(OtBu), with X = D.Ser (OtBu) in BUBU and X = D.Cys(StBu) in BUBUC, and complete inhibitors of enkephalin metabolism (Kelatorphan, RB 38 A, RB 101) have enabled the major role played by μ-opioid receptors in supraspinal analgesia to be demonstrated. This is in agreement with the results of in vivo μ receptor occupancy measured by taking into account the cross-reactivity of the δ ligands for μ sites. In contrast μ and δ binding sites seem to act independently to control **pain** at the spinal level. The selective μ2 agonist TRIMU-5 induces strong antinociceptive responses by acting at the spinal level. Potent analgesic effects, especially in arthritic rats, can also be obtained by complete protection of tonically or phys. released endogenous enkephalins with mixed inhibitors such as RB 38 A. Chronic i.c.v. administration of the agonist DAMGO, led to a severe naloxone precipitated withdrawal syndrome while a weak dependence was seen with the agonist, DSTBULET or with RB 38 A and none after repeated i.p. injection of RB 101 a systemically active mixed inhibitor. Moreover chronic administration of RB 101 did not induce psychic dependence, a major side effect of morphine. These differences could be related to a more efficient and selective stimulation of opioid receptors by the endogenous enkephalins at the level of brain structures involved in **pain** control. This suggests that the large changes in receptor d., adenylate cyclase activity or phosphorylation of proteins induced by chronic morphine is not significantly triggered by occupation of the opioid receptors by their natural ligands. All these data emphasize the interest in developing δ agonists and mixed inhibitors with appropriate bioavailable for clin. evaluation.

L38 ANSWER 46 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1997:209403 HCAPLUS
DOCUMENT NUMBER: 126:259227
TITLE: Opioid and non-opioid interactions in the control of nociception in the dorsal horn
AUTHOR(S): Dickenson, A.; Stanfa, L.; Chapman, V.
CORPORATE SOURCE: Dept. of Pharmacology, University College London, London, WC1E 6BT, UK
SOURCE: Neuropeptides, Nociception, and Pain, Symposium, Mainz, Oct. 8-10, 1992 (**1994**), Meeting Date 1992, 243-262. Editor(s): **Hoekfelt, Tomas; Schaible, Hans-Georg; Schmidt, Robert F.** Chapman & Hall: London, UK.
CODEN: 64DPAS
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review, with .apprx.84 refs. Topics discussed include: opioid controls on nociceptive transmission in the dorsal horn, opioid receptors and endogenous opioids in the spinal cord, functional roles of opioid receptors in spinal antinociception, opioid mechanisms of spinal antinociception, interactions between segmental modulatory systems and changes in opioid controls at the spinal level, opioid interactions with cholecystokinin and FLFQPQRFamide, opioid interactions with NMDA receptor induced activity, opioid interactions with descending noradrenergic controls and opioid interactions with dynorphin.

L38 ANSWER 47 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:209401 HCAPLUS
DOCUMENT NUMBER: 126:259226
TITLE: Roles of substance P in spinal nociceptive pathways
AUTHOR(S): Henry, J. L.
CORPORATE SOURCE: Departments of Physiology and Psychiatry, McGill University, Montreal, QC, Can.
SOURCE: Neuropeptides, Nociception, and Pain, Symposium, Mainz, Oct. 8-10, 1992 (**1994**), Meeting Date 1992, 209-220. Editor(s): **Hoekfelt, Tomas; Schaible, Hans-Georg; Schmidt, Robert F.** Chapman & Hall: London, UK.
CODEN: 64DPAS
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review, with .apprx.48 refs. Topics discussed include: evidence implicating substance P in mediation of sensory inputs, electrophysiol. studies on effects of NK-1 receptor antagonists on substance P-induced excitation of dorsal horn neurons and on excitation of dorsal horn neurons by noxious cutaneous stimuli, and correlation of electrophysiol. results with immunocytochem.

L38 ANSWER 48 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:209400 HCAPLUS
DOCUMENT NUMBER: 126:259505
TITLE: Changes in excitability induced by substance P in dorsal horn neurons and non-myelinated primary afferent units
AUTHOR(S): Mense, S.; Hoheisel, U.; Reinert, A.
CORPORATE SOURCE: Institut fur Anatomie und Zellbiologie, Heidelberg, D-69120, Germany
SOURCE: Neuropeptides, Nociception, and Pain, Symposium, Mainz, Oct. 8-10, 1992 (**1994**), Meeting Date 1992, 199-208. Editor(s): **Hoekfelt, Tomas; Schaible, Hans-Georg; Schmidt, Robert F.** Chapman

& Hall: London, UK.
CODEN: 64DPAS
DOCUMENT TYPE: Conference
LANGUAGE: English
AB The influence of substance P on discharge behavior of slowly conducting primary afferent neurons in skeletal muscle and on the excitability of dorsal horn neurons was studied in rats. The action of substance P on nonmyelinated primary afferents from the diaphragm was characterized by a combination of increased background activity in nociceptive receptors and a decreased mech. sensitivity in non-nociceptive units. Superfusion of the spinal cord with substance P had heterogeneous effects on the elec. excitability of dorsal horn neurons with the main action being a change in the input a given neuron responded to. Substance P may not only be involved in hyperalgesia but also in neuroplastic changes that eventually may lead to the transition from acute to chronic **pain.**

L38 ANSWER 49 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:209399 HCAPLUS
DOCUMENT NUMBER: 126:259504
TITLE: Interactions between excitatory amino acids and tachykinins and long-term changes of synaptic responses in the rat spinal dorsal horn
AUTHOR(S): Rusin, K. I.; Jiang, M. C.; Cerne, R.; Kolaj, M.; Randic, M.
CORPORATE SOURCE: Dep. Vet. Physiol. Pharmacol., Iowa State Univ., Ames, IA, 50011, USA
SOURCE: Neuropeptides, Nociception, and Pain, Symposium, Mainz, Oct. 8-10, 1992 (**1994**), Meeting Date 1992, 163-197. Editor(s): **Hoekfelt, Tomas; Schaible, Hans-Georg; Schmidt, Robert F.** Chapman & Hall: London, UK.
CODEN: 64DPAS
DOCUMENT TYPE: Conference
LANGUAGE: English
AB The whole-cell patch-clamp technique of freshly isolated rat spinal dorsal horn (DH) neurons, intracellular recording from DH neurons in a slice preparation, and HPLC with fluorimetric detection of release of endogenous glutamate and aspartate from spinal cord slice following activation of primary afferent fibers, were employed to investigate interactions between excitatory amino acids (EAA) and tachykinins [substance P (SP) and neurokinin A (NKA)]. Potentiation of N-methyl-D-aspartate (NMDA)-, quisqualate (QA)- and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-, but not kainate-induced currents by SP and NKA was found. Spantide II, a claimed novel non-selective tachykinin antagonist, effectively blocked the SP-induced potentiation of the responses of DH neurons to NMDA. In the presence of glycine, the SP-evoked increase of the NMDA-induced current was prevented. However, 7-chlorokynurenic acid, a competitive antagonist at the glycine allosteric site of the NMDA receptor, led to the re-establishment of the SP effect. Phorbol esters and forskolin, after an initial small depression enhanced the NMDA-induced current, and staurosporine, the agent known to inhibit both protein kinase C and cAMP-dependent protein kinase, reduced the potentiation of NMDA responses of DH cells by tachykinins. It is concluded that activation of protein kinases, especially protein kinase C, may mediate the enhancement of the NMDA responses of DH cells. Brief high frequency elec. stimulation of primary afferent fibers produced a long-lasting potentiation and a long-lasting depression of presumed monosynaptic and polysynaptic excitatory postsynaptic pot. in the superficial spinal DH. The same tetanic stimulation can induce either potentiation or depression depending on the level of depolarization of the

postsynaptic neuron. Both the AMPA and the NMDA receptor-mediated components of synaptic transmission at the primary afferent synapses with neurons in the rat superficial spinal DH can exhibit the prolonged potentiation and depression of the synaptic responses. In both normal and neonatally capsaicin-treated rats, the induction of the potentiation requires the activation of NMDA receptor-gated conductances. However, the induction of the long-lasting potentiation or depression was not abolished in the presence of bicuculline, a GABAA receptor antagonist. Long-lasting potentiation of the excitatory synaptic transmission in the spinal DH is associated with increased and prolonged glutamate and aspartate release. Apparently, distinct and long-lasting changes in synaptic efficacy can be induced by high frequency stimulation of primary afferents and integration of sensory information, including **pain.**

L38 ANSWER 50 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:209397 HCAPLUS
DOCUMENT NUMBER: 126:247118
TITLE: Participation of neuropeptides in spinal mechanisms of inflammation- and stress-induced hyperalgesia
AUTHOR(S): Kuraishi, Y.; Satoh, M.
CORPORATE SOURCE: Department of Applied Biochemistry, Research Institute for Wakan-yaku, Toyama Medical and Pharmaceutical University, Toyama, 930-01, Japan
SOURCE: Neuropeptides, Nociception, and Pain, Symposium, Mainz, Oct. 8-10, 1992 (**1994**), Meeting Date 1992, 127-139. Editor(s): **Hoekfelt, Tomas; Schaible, Hans-Georg; Schmidt, Robert F.** Chapman & Hall: London, UK.
CODEN: 64DPAS
DOCUMENT TYPE: Conference
LANGUAGE: English
AB The authors investigated whether substance P (SP), galanin (GAL), and CGRP are involved in hyperalgesia produced by peripheral inflammation and repeated cold stress (RCS). To this end, the effects of intrathecal injections of antibodies to these neuropeptides on hyperalgesia induced by carrageenin inflammation and RCS were examined Addnl., interactions of GAL and CGRP with SP in the spinal cord was investigated. Results suggest a role for CGRP in facilitation of nociceptive transmission, especially SP-mediated transmission, in the spinal dorsal horn.

L38 ANSWER 51 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:209395 HCAPLUS
DOCUMENT NUMBER: 126:246862
TITLE: Expression of neuropeptides, neuropeptide receptors and neuropeptide processing enzymes in spinal neurons and peripheral non-neural cells and plasticity in models of inflammatory **pain**
AUTHOR(S): Weihe, E.; Schaefer, M. K.-H.; Nohr, D.; Persson, S.
CORPORATE SOURCE: Anatomical Institute, University of Mainz, Mainz, D-55122, Germany
SOURCE: Neuropeptides, Nociception, and Pain, Symposium, Mainz, Oct. 8-10, 1992 (**1994**), Meeting Date 1992, 43-69. Editor(s): **Hoekfelt, Tomas; Schaible, Hans-Georg; Schmidt, Robert F.** Chapman & Hall: London, UK.
CODEN: 64DPAS
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review, with .apprx.100 refs., of neurochem. changes along the neuroaxis serving nociception and possibly antinociception. Also discussed was the

pharmacol. modulability of inflammation-induced changes of neuropeptide and immediate early gene expression as a monitor of cytoanatomically definable drug effects. The main focus is on the spinal cord and the inflamed tissue in the periphery.

L38 ANSWER 52 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:209394 HCAPLUS
DOCUMENT NUMBER: 126:262737
TITLE: Neuropeptides in primary afferents from normal and inflamed joints
AUTHOR(S): Heppelmann, B.; Hanesch, U.; Schmidt, R. F.
CORPORATE SOURCE: Physiologisches Institut der Universitat Wurzburg, Wurzburg, D-97070, Germany
SOURCE: Neuropeptides, Nociception, and Pain, Symposium, Mainz, Oct. 8-10, 1992 (**1994**), Meeting Date 1992, 33-42. Editor(s): **Hoekfelt, Tomas; Schaible, Hans-Georg; Schmidt, Robert F.** Chapman & Hall: London, UK.
CODEN: 64DPAS
DOCUMENT TYPE: Conference
LANGUAGE: English
AB The influence of acute and chronic arthritis on the proportion of primary afferents containing neuropeptides was studied in feline joints. Combined morphol., physiol. and immunohistochem. studies indicated that in a normal joint the majority of the primary afferents are nociceptors, whereas some act as mechanosensors; only a small proportion contain the neuropeptides substance P, neurokinin A, CGRP and somatostatin. In an inflamed joint most of the nociceptors afferents become mechanosensors, and a higher number of afferents contain substance P and CGRP, whereas the proportion of somatostatin-synthesizing neurons seems to be unaffected.

L38 ANSWER 53 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:177049 HCAPLUS
DOCUMENT NUMBER: 126:223589
TITLE: Neurophysiology of chronic inflammatory **pain** : electrophysiological recordings from spinal cord neurons in rats with prolonged acute and chronic unilateral inflammation at the ankle
AUTHOR(S): **Schaible, Hans-Georg**; Schmidt, Robert F.
CORPORATE SOURCE: Physiologisches Institut der Universitat Wurzburg, Wurzburg, D-97070, Germany
SOURCE: Progress in Brain Research (**1996**), 110(Towards the Neurobiology of Chronic Pain), 167-176
CODEN: PBRRA4; ISSN: 0079-6123
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 57 refs., of evidence that the nociceptive processing in the spinal cord under chronic inflammatory conditions exhibits numerous phenomena which are also seen during acute inflammation of the knee joint. Excitatory amino acids and their NMDA and non-NMDA receptors are similarly involved in nociceptive processing under conditions of acute, prolonged and chronic inflammation. An upregulation of κ-opioid system has been found in both acute and chronic inflammation and CGRP synthesis is upregulated during inflammation.

L38 ANSWER 54 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:177003 HCAPLUS
DOCUMENT NUMBER: 126:220736
TITLE: On the role of tachykinins and calcitonin gene-related

peptide in the spinal mechanisms of nociception and in the induction and maintenance of inflammation-evoked hyperexcitability in spinal cord neurons (with special reference to nociception in joints)

AUTHOR(S): **Schaible, Hans-Georg**
CORPORATE SOURCE: Physiologisches Institut, Universitat Wurzburg, Wurzburg, D-97070, Germany
SOURCE: Progress in Brain Research (**1996**), 113(Polymodal Receptor: A Gateway to Pathological Pain), 423-441
CODEN: PBRRA4; ISSN: 0079-6123
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review, with 133 refs. The author addresses the functional role of substance P (SP), neurokinin A (NKA) and calcitonin gene-related peptide (CGRP) and their receptors in the spinal processing of nociceptive information with special reference to nociception in the joint. The role of SP, NKA and CGRP and their receptors in the generation and maintenance of inflammation-evoked hyperexcitability of spinal cord neurons is also discussed.

L38 ANSWER 55 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:176994 HCAPLUS
DOCUMENT NUMBER: 126:236763
TITLE: Interactions of sympathetic and primary afferent neurons following nerve injury and tissue trauma
AUTHOR(S): Jaenig, W.; Levine, J.D.; **Michaelis, M.**
CORPORATE SOURCE: Physiologisches Institut, Christian-Albrechts-Universitat zu Kiel, Kiel, 24098, Germany
SOURCE: Progress in Brain Research (**1996**), 113(Polymodal Receptor: A Gateway to Pathological Pain), 161-184
CODEN: PBRRA4; ISSN: 0079-6123
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 93 refs. Topics discussed include: clin. evidence for a sympathetic nervous system contribution to **pain** states, coupling between sympathetic post-ganglionic neurons and primary afferent neurons following peripheral nerve lesion, indirect coupling between noradrenergic nerve terminals and nociceptors in the periphery, and involvement of the sympathetic nervous system in hyperalgesia and neurogenic inflammation.

L38 ANSWER 56 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:133702 HCAPLUS
DOCUMENT NUMBER: 126:155371
TITLE: Neurobiology of articular nociceptors
AUTHOR(S): **Schaible, Hans-Georg**; Schmidt, Robert F.
CORPORATE SOURCE: Physiologisches Institut, Universitaet Wuerzburg, Wuerzburg, 97070, Germany
SOURCE: Neurobiology of Nociceptors (**1996**), 202-219.
Editor(s): Belmonte, Carlos; Cervero, Fernando.
Oxford University Press: Oxford, UK.
CODEN: 63ZSA4
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English

AB A review and discussion with several refs. Morphol. of articular nociceptors, response properties of articular afferents, action of chemical modulators, peptidergic functions of articular afferents were discussed.

L38 ANSWER 57 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:92192 HCAPLUS
DOCUMENT NUMBER: 126:166418
TITLE: Effects of N- and L-type calcium channel antagonists on the responses of nociceptive spinal cord neurons to mechanical stimulation of the normal and the inflamed knee joint
AUTHOR(S): Neugebauer, V.; Vanegas, H.; Nebe, J.; Ruemenapp, P.; **Schaible, H.-G.**
CORPORATE SOURCE: Physiologisches Institut, Universitat Wurzburg, Wurzburg, D-97070, Germany
SOURCE: Journal of Neurophysiology (**1996**), 76(6), 3740-3749
CODEN: JONEA4; ISSN: 0022-3077
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB 1. The present study addresses the involvement of voltage-dependent calcium channels of the N and L type in the spinal processing of innocuous and noxious input from the knee joint, both under normal conditions and under inflammatory conditions in which spinal cord neurons become hyperexcitable. In 30 anesthetized rats, extracellular recordings were performed from single dorsal horn neurons in segments 1 -4 of the lumbar spinal cord. All neurons had receptive fields in the ipsilateral knee joint. In 22 rats, an inflammation was induced in the ipsilateral knee joint by kaolin and carrageenan 4- 16 h before the recordings. The antagonist at N-type calcium channels, ω-conotoxin GVIA (ω-CTx GVIA), was administered topically in solution to the dorsal surface of the spinal cord at the appropriate spinal segments in 6 rats with normal joints and in 12 rats with inflamed knee joints. The antagonist at L-type channels, nimodipine, was administered topically in 5 rats with normal joints and in 11 rats with inflamed knee joints. In another five rats with inflamed joints, antagonists at L-type calcium channels (diltiazem and nimodipine) and ω-CTx GVIA were administered ionophoretically with multibarrel electrodes close to the neurons recorded. 2. The topical administration of ω-CTx GVIA to the spinal cord reduced the responses to both innocuous and noxious pressure applied to the knee joint in a sample of 11 neurons with input from the normal joint and in a sample of 16 neurons with input from the inflamed joint (hyperexcitable neurons). The responses were decreased to .apprx.65% of the predrug values within administration times of 30 min. A similar reduction of the responses to innocuous and noxious pressure was observed when ω-CTx GVIA was administered ionophoretically to nine hyperexcitable neurons. In neurons with input from the normal or the inflamed knee joint, the administration of ω-CTx GVIA led also to a reduction of the responses to innocuous and noxious pressure applied to the noninflamed ankle joint. 3. The topical administration of nimodipine decreased the responses to innocuous and noxious pressure applied to the knee in a sample of 9 neurons with input from the normal joint and in a sample of 16 neurons with input from the inflamed knee joint (hyperexcitable neurons). Within administration times of 30 min, the responses were reduced to .apprx.70% of the predrug values. In hyperexcitable neurons, the responses to innocuous and noxious pressure applied to the knee were also decreased during ionophoretic administration of nimodipine (6 neurons) and diltiazem (9 neurons). When the noninflamed ankle was stimulated, the responses to innocuous pressure were reduced neither in neurons with input from the normal knee nor in neurons with input from the inflamed knee, but the responses of hyperexcitable neurons to noxious pressure onto the ankle were reduced. The ionophoretic administration of the agonist at the L-type calcium channel, S(-)-Bay K

8644, enhanced the responses to mech. stimulation of the knee joint in all 14 hyperexcitable neurons tested. The effect of S(-)-Bay K 8644 was counteracted by both diltiazem (in 6 of 6 neurons) and nimodipine (in 5 of 5 neurons). 4. These data show that antagonists at both the N- and the L-type voltage-dependent calcium channels influence the spinal processing of input from the knee joint. The data suggest, therefore, that voltage-dependent calcium channels of both the N and the L type are important for the sensory functions of the spinal cord. They are involved in the spinal processing of non-nociceptive as well as nociceptive mechanosensory input from the joint, both under normal and inflammatory conditions. The present results show in particular that N- and L-type channels are likely to be involved in the generation of **pain** evoked by noxious mech. stimulation in normal tissue as well as in the mech. hyperalgesia that is usually present during inflammation.

REFERENCE COUNT: 69 THERE ARE 69 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 58 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1996:762106 HCAPLUS
DOCUMENT NUMBER: 126:84973
TITLE: Release of immunoreactive substance P in the trigeminal brain stem nuclear complex evoked by chemical stimulation of the nasal mucosa and the dura mater encephali - a study with antibody microprobes
AUTHOR(S): **Schaible, H.-G.**; Ebersberger, A.; Peppel, P.; Beck, U.; Messlinger, K.
CORPORATE SOURCE: Physiologisches Institut, Universitaet Wuerzburg, Wuerzburg, D-97070, Germany
SOURCE: Neuroscience (Oxford) (**1996**), Volume Date 1997, 76(1), 273-284
CODEN: NRSCDN; ISSN: 0306-4522
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In order to study a possible involvement of substance P in the processing of chemonociceptive input from the nasal mucosa and the dura mater encephali in the spinal trigeminal, the release of immunoreactive substance P was measured in the trigeminal brain stem nuclear complex in anesthetized rats. Microprobes coated with antibody to substance P were inserted into the lateral area of the brain stem up to 1 mm posterior to the obex corresponding to the trigeminal subnucleus caudalis. When the nasal mucosa was stimulated by topical administration of mustard oil (1% and 5%) into the nostrils, immunoreactive substance P was mainly detected in the dorsal region of the trigeminal brain stem nuclear complex with a maximum in the superficial gray matter. When the dura mater encephali was stimulated by topical administration of Tyrode's solution (pH 6.2), immunoreactive substance P was mainly released in the ventral region of the trigeminal brain stem nuclear complex; with pH 5.5 the release was more diffuse extending from the ventral to the dorsal part of the spinal trigeminal nucleus. Release was maximal rather after than during the administration of the stimuli, and it considerably out-lasted the stimulation periods. These data suggest that substance P plays an important role in the processing of chemonociceptive inputs from the nasal mucosa and the dura mater encephali in the trigeminal brain stem nuclear complex. Substance P may be important, therefore, in the generation of those headaches that are caused by affections of the nasal mucosa and the dura mater encephali. Since enhanced levels of immunoreactive substance P were present for considerable time periods beyond the administration of the stimuli, substance P and neurokinin-1 receptors may be involved in long-lasting neuronal events following noxious stimulation.

REFERENCE COUNT: 79 THERE ARE 79 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 59 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:484890 HCAPLUS
DOCUMENT NUMBER: 125:164916
TITLE: Up-regulation of cyclooxygenase-2 mRNA in the rat spinal cord following peripheral inflammation
AUTHOR(S): Beiche, Flora; Scheuerer, Stefan; Brune, Kay; **Geisslinger, Gerd**; Goppelt-Struebe, Margarete
CORPORATE SOURCE: Dep. Exp. Clinical Pharmacol. Toxicol., Univ. Erlangen-Nuernberg, Erlangen, D-91054, Germany
SOURCE: FEBS Letters (**1996**), 390(2), 165-169
CODEN: FEBLAL; ISSN: 0014-5793
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Prostaglandins (PG) have been described as mediators in spinal nociceptive processing after peripheral inflammation. Enzymes essential for PG biosynthesis, cyclooxygenase isoenzymes COX-1 and COX-2, have not yet been investigated in the spinal cord. In two studies on rats with adjuvant-induced peripheral inflammation levels of mRNA expression of both COx isoforms were analyzed in the lumbar section of the spinal cord using reverse transcription-polymerase chain reaction (RT-PCR) technique. We could show that mRNA of both COX isoforms is expressed constitutively in the spinal cord with COX-2 as the predominant isoform. Six hours after induction of peripheral inflammation, levels of COX-2 mRNA expression were raised significantly in respect to untreated control rats and returned to baseline within 3 days after induction of inflammation. COX-2 might therefore be regarded as the COX isoenzyme responsible for spinal PG release in nociceptive processing under a peripheral inflammatory stimulus.

L38 ANSWER 60 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:282606 HCAPLUS
DOCUMENT NUMBER: 125:5915
TITLE: Silent afferents: a separate class of primary afferents?
AUTHOR(S): **Michaelis, M.**; Haebler, H.-J.; Jaenig, W.
CORPORATE SOURCE: Physiologisches Inst., Christian-Albrechts-Univ., Kiel, Germany
SOURCE: Clinical and Experimental Pharmacology and Physiology (**1996**), 23(2), 99-105
CODEN: CEXPB9; ISSN: 0305-1870
PUBLISHER: Blackwell
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 79 refs., on silent afferent nerves. In recent years, fine sensory nerve fibers have been detected that are not excited by physiol. stimuli, even at potentially tissue damaging intensities. These silent afferents are known to supply knee joint, skin and viscera; in the last case, silent afferents seem to be particularly numerous. When an artificial inflammation is induced, many silent afferents develop spike activity, others remain quiescent. Silent afferents that do respond probably have a nociceptive sensory function. Under inflammatory conditions some silent afferents are sensitized to physiol. stimuli, others are probably chemospecific. Orthodromic activity in silent afferents may sum spatially and temporally in second order neurons with other nociceptive information and may thereby contribute to different **pain** states. Furthermore, there is evidence that the activation

of chemospecific silent afferents may lead to sensitization of nociceptive dorsal horn neurons. Some silent afferents probably contain neuropeptides that may be liberated under pathophysiol. conditions, such as inflammation. Whether certain pathol. states can be exclusively attributed to the activation of silent afferents or whether silent afferents sustain the functions of "conventional" nociceptors remains to be clarified.

L38 ANSWER 61 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:107981 HCAPLUS
DOCUMENT NUMBER: 124:220227
TITLE: Effects of azapropazone on **pain**-related brain activity in human subjects
AUTHOR(S): Loetsch, Joern; Mohammadian, Parvaneh; Hummel, Thomas; Florin, Sabine; Brune, Kay; **Geisslinger, Gerd**; Kobal, Gerd
CORPORATE SOURCE: Department Experimental and Clinical Pharmacology and Toxicology, University Erlangen-Nurnberg, Erlangen, D-91054, Germany
SOURCE: British Journal of Clinical Pharmacology (**1995**), 40(6), 545-52
CODEN: BCPHBM; ISSN: 0306-5251
PUBLISHER: Blackwell
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The dose-related effects of azapropazone on (i) event-related and spontaneous EEG-activity and (ii) the subjects' **pain** ratings were investigated using an exptl. human **pain** model based on both chemo-somatosensory event-related potentials (CSSERP) and subjects' **pain** ratings. Healthy subjects (n=20) participated in a placebo-controlled, randomized, double-blind, four-way cross-over study. Single doses of azapropazone (300 mg, 600 mg and 1200 mg) and placebo were administered i.v. Each experiment consisted of five sessions (before and 1, 2, 4 and 8 h after administration of the medication). Each session lasted for approx. 40 min. In the first 20 min, **pain** was induced by short CO2-stimuli presented to the right nostril (phasic **pain**; interstimulus interval 30 s) and EEG was recorded from five positions. CSSERPs were obtained in response to painful CO2-stimuli. In the following 20 min period, tonic **pain** was induced by a constant stream of dry air introduced in the left nostril. Subjects rated the intensity of both phasic and tonic **pain** by means of a visual analog scale. Addnl., a frequency anal. of the spontaneous EEG was performed. Azapropazone reduced the **pain**-related CSSERP-amplitudes at frontal and parietal recording positions. This topog. pattern was observed in previous studies with opioids, while NSAIDs such as flurbiprofen and ketoprofen exerted effects at frontal and central positions. In contrast to other NSAIDs, administration of azapropazone resulted in a reduction of the frequency bands alpha1, delta and theta of the spontaneous EEG. At the subjective level, analgesic effects of azapropazone were observed in the ratings of tonic **pain.** Analgesic properties of azapropazone were demonstrated in man. The topog. pattern of the changes in the CSSERPs and the effects on EEG background activity suggest a central component of the analgesic action of azapropazone.

L38 ANSWER 62 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:971823 HCAPLUS
DOCUMENT NUMBER: 124:75876
TITLE: Effects of flurbiprofen enantiomers on **pain**-related chemo-somatosensory evoked potentials in human subjects

AUTHOR(S): Loetsch, Joern; **Geisslinger, Gerd**; Mohammadian, Parvaneh; Brune, Kay; Kobal, Gerd
CORPORATE SOURCE: Department Experimental and Clinical Pharmacology and Toxicology, University Erlangen-Nurnberg, Erlangen, D-91054, Germany
SOURCE: British Journal of Clinical Pharmacology (**1995**), 40(4), 339-46
CODEN: BCPHBM; ISSN: 0306-5251
PUBLISHER: Blackwell
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The aim of the study was to investigate the analgesic effects of flurbiprofen enantiomers using an exptl. **pain** model based on both chemo-somatosensory event-related potentials (CSSERP) and subjective **pain** ratings. Healthy female volunteers (age 23-36 yr) participated in a placebo-controlled, randomized, double-blind, four-way crossover study. Single doses of (S)-flurbiprofen (50 mg), (R)-flurbiprofen (50 and 100 mg) and placebo were administered orally. Measurements were taken before and 2 h after administration of the medications. During each measurement, 32 painful stimuli of gaseous carbon dioxide (200 ms duration, interval approx. 30 s) of two concns. (60 and 65% CO2 volume/volume) were applied to the right nostril. EEG was recorded from five positions and CSSERP were obtained in response to the painful CO2-stimuli. Addnl., subjects rated the perceived intensity of the painful stimuli by a visual analog scale (VAS). The CSSERP-amplitude P2, a measure of analgesic effect, decreased after administration of both (R)- and (S)-flurbiprofen, while it increased after placebo. This was statistically significant at recording positions C4 and Fz. The analgesia-related decreases in evoked potential produced by (R)-flurbiprofen were dose-dependent. Comparing similar doses of (R)- and (S)-flurbiprofen, the decrease in CSSERP-amplitudes produced by the (S)-enantiomer was somewhat more pronounced, indicating a higher analgesic potency. The present data indicate that both enantiomers of flurbiprofen produce analgesic effects. Since (R)-flurbiprofen caused only little toxicity in rats as compared with the (S)-enantiomer or the racemic compound, a reduction of the quant. most important side effects in the gastrointestinal tract might be achieved by employing (R)-flurbiprofen in **pain** therapy.

L38 ANSWER 63 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:837813 HCAPLUS
DOCUMENT NUMBER: 123:246295
TITLE: Inflammatory models of cutaneous hyperalgesia are sensitive to effects of ibuprofen in man
AUTHOR(S): Kilo, S.; Forster, C.; **Geisslinger, G.**; Brune, K.; Handwerker, H.O.
CORPORATE SOURCE: Department of Physiology I, University of Erlangen-Nuernberg, Erlangen, D-91054, Germany
SOURCE: Pain (**1995**), 62(2), 187-93
CODEN: PAINDB; ISSN: 0304-3959
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A new exptl. procedure was developed to quantify the analgesic actions of non-steroidal anti-inflammatory drugs (NSAIDs) in healthy human subjects. To mimic the clin. situation, the drug was 'therapeutically' administered 1 day after induction of inflammation by freezing a small skin area. The procedure was easily tolerated and led to a marked hyperalgesia without ongoing **pain** which was tested using mech. impact stimulation and magnitude estimation For comparison, the authors used a previously established

model of repeated noxious pinching of an interdigital skin web which induces a hyperalgesia to pressure (rated via visual analog scale), and topical application of capsaicin which leads to quantifiable flare and allodynia responses. The effects of a cumulative drug regime of ibuprofen in 2 different doses (3+400 mg and 3+800 mg at 2-h intervals) were tested vs. placebo using a double-blind cross-over design with 24 volunteers of either gender. Ibuprofen caused a significant suppression of the hyperalgesia to repeated pinching and of the hyperalgesia to impact stimulation following freeze trauma. In contrast, there was no effect on the areas of flare and allodynia induced by capsaicin application and on the impact evoked sensations from untreated skin. The two dosages of ibuprofen, however, appeared to be equally effective in a way that suggests a plateauing of the antihyperalgesic effect. The two models in which hyperalgesia is affected by ibuprofen, i.e., repeated pinching and impact stimulation after freeze trauma, seem to provide comparable sensitivity. The freeze model may in the future have the advantage to allow for a better temporal resolution of the drug's action profile.

L38 ANSWER 64 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:820811 HCAPLUS
DOCUMENT NUMBER: 123:208870
TITLE: Pharmaceutical compositions containing tiaprofenic acid enantiomers for treatment of **pain**, inflammation, and fever
INVENTOR(S): **Geisslinger, Gerd**; Brune, Kay
PATENT ASSIGNEE(S): Germany
SOURCE: Ger. Offen., 5 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 4404399	A1	19950817	DE 1994-4404399	19940211 <--
PRIORITY APPLN. INFO.:			DE 1994-4404399	19940211

AB The title pharmaceutical compns. for human or veterinary use contain the separated enantiomers of tiaprofenic acid alone or as a recombined mixture The recombined mixture shows a higher release rate than the racemate. Combinations containing a preponderance of R(-)-tiaprofenic acid show a min. of side effects. Analgesic compns. preferably contain 60-100% R(-)-tiaprofenic acid, and antiinflammatory compns. preferably contain 60-100% S(+)-tiaprofenic acid.

L38 ANSWER 65 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:574930 HCAPLUS
DOCUMENT NUMBER: 122:307027
TITLE: Involvement of substance P and neurokinin-1 receptors in the hyperexcitability of dorsal horn neurons during development of acute arthritis in rat's knee joint
AUTHOR(S): Neugebauer, V.; Weiretter, F.; **Schaible, H.-G.**
CORPORATE SOURCE: Physiologisches Institut, Universitaet Wuerzburg, Wuerzburg, D-97070, Germany
SOURCE: Journal of Neurophysiology (**1995**), 73(4), 1574-83
CODEN: JONEA4; ISSN: 0022-3077
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In anesthetized rats the authors studied the involvement of substance P

and neurokinin-1 receptors in the generation and maintenance of hyperexcitability in spinal cord neurons, which develops in the course of an acute exptl. inflammation in the knee. In all expts. one nociceptive neuron with knee input was identified, and the responses to mech. stimuli and the receptive fields were monitored before and after induction of inflammation by the injections of kaolin and carrageenan into the knee joint. In 18 expts. either the specific antagonist at the neurokinin-1 receptor, CP96,345, or the inactive enantiomer, CP96,344, was administered iontophoretically close to the neuron or i.v. during the injections of kaolin and carrageenan and in three periods of 15 min in the 95 min post-kaolin (initial period of inflammation) to test their effects on the development of hyperexcitability. CP96,345 and CP96,344 were also administered after full development of inflammation to study their effects in hyperexcitable neurons. CP96,345 was ejected at currents that reduced or completely suppressed the effects of iontophoretically administered substance P but not those of neurokinin A, the agonist at neurokinin-2 receptors. After the injections of kaolin and carrageenan into the knee joint, untreated control neurons developed hyperexcitability consisting of enhanced responses to noxious stimuli applied to the injected knee and the non-injected ankle, of an enhancement or induction of the responses to innocuous pressure applied to the joints and of an expansion of the receptive field. In eight neurons treated with ionophoretic administration of CP96,345 during the induction and initial period of inflammation, the development of hyperexcitability was not completely prevented but significantly attenuated. In comparison with the changes in the control neurons, the development of hyperexcitability was markedly reduced from the 2nd h up to 5 h post-kaolin, but it was barely affected by CP96,345 within the 1st h post-kaolin. I.v. administration of CP96,345 in the initial period of inflammation produced a similar reduction of the development of hyperexcitability in another four neurons. The ionophoretic application of CP96,344 during and after induction of inflammation did not apparently impair the development of hyperexcitability (neurons). After development of inflammation and hyperexcitability, both the responses to innocuous and noxious pressure applied to the inflamed knee joint were reduced by the ionophoretic (neurons) and i.v. administration (neurons) of CP96,345 (tested 4.5-8 h post-kaolin). Similarly, the responses to innocuous and noxious pressure applied to the non-inflamed ankle were reduced by CP96,345 after inflammation had developed in the knee joint. In 10 of 16 hyperexcitable neurons, the administration of CP96,345 reduced the size of the receptive field. None of the effects of CP96,345 was mimicked by the ionophoretic administration of CP96,344 in 16 hyperexcitable neurons tested. In summary, the administration of the neurokinin-1 antagonist CP96,345 in the initial period of inflammation attenuated the development of inflammation-evoked hyperexcitability in spinal cord neurons without preventing initial changes of excitability to mech. stimuli within the 1st h after induction of inflammation. Thus release of substance P and activation of neurokinin-1 receptors do not seem to be necessary for the initial changes of responsiveness of spinal cord neurons, but this transmitter/receptor system apparently needs to be activated at an early stage for the further progression of hyperexcitability in this model of inflammation. The continuous activation of neurokinin-1 receptors seems to be involved in the maintenance of the inflammation-evoked discharges because the application of CP96,345 also reduced the responses to innocuous and noxious pressure and the size of expanded receptive fields after expression of hyperexcitability. These data show, therefore, an important role of neurokinin-1 receptors and substance P in the nociceptive processing in the spinal cord underlying the (enhanced) painfulness of inflamed joints.

L38 ANSWER 66 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:252817 HCAPLUS
DOCUMENT NUMBER: 122:24402
TITLE: The involvement of substance P and neurokinin-1 receptors in the responses of rat dorsal horn neurons to noxious but not to innocuous mechanical stimuli applied to the knee joint
AUTHOR(S): Neugebauer, Volker; **Schaible, Hans-Georg**; Weiretter, Frank; Freudenberger, Ulrike
CORPORATE SOURCE: Physiologisches Institut, Universitaet Wuerzburg, Roentgenring 9, Wurzburg, D-97070, Germany
SOURCE: Brain Research (**1994**), 666(2), 207-15
CODEN: BRREAP; ISSN: 0006-8993
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In 29 anesthetized rats, the involvement of substance P and neurokinin-1 receptors in the spinal processing of mechanosensory innocuous and noxious information from the knee and ankle joint was investigated. In 21 rats, multibarrel electrodes were used to record from 46 spinal cord neurons with afferent input from the knee joint and to administer agonists and antagonists by microionophoresis. In 35 of 46 nociceptive neurons, substance P (ejected at 20-120 nA) caused an excitation and/or an increase in responses to innocuous and noxious pressure applied to the knee and ankle. These effects were reduced by ionophoretic application of the specific neurokinin-1 receptor antagonist CP96,345 (ejected at 25-80 nA) but not by CP96,344, its inactive enantiomer. CP96,345 dose-dependently reduced the responses to noxious pressure applied to the knee joint in 28/28 substance P-sensitive neurons but not those to innocuous pressure in 23/23 substance P-sensitive wide dynamic range neurons. CP96,345 did not affect responses to pressure in substance P-insensitive neurons and the inactive enantiomer CP96,344 had no effect in any of the neurons tested. Using microprobes coated with antibody to substance P, intraspinal release of immunoreactive substance P was evoked by noxious pressure applied to the knee but not by innocuous pressure in 8 rats. Both sets of data suggest a role for substance P and neurokinin-1 receptors in the neuronal mechanisms in the spinal cord related to nociception and **pain** in the normal joint.

L38 ANSWER 67 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:188884 HCAPLUS
DOCUMENT NUMBER: 122:7160
TITLE: Intraspinal release of immunoreactive calcitonin gene-related peptide during development of inflammation in the joint in vivo-a study with antibody microprobes in cat and rat
AUTHOR(S): **Schaible, H.-G.**; Freudenberger, U.; Neugebauer, V.; Stiller, R. U.
CORPORATE SOURCE: Physiol. Inst., Universitaet Wuerzburg, Wuerzburg, D-97070, Germany
SOURCE: Neuroscience (Oxford) (**1994**), 62(4), 1293-305
CODEN: NRSCDN; ISSN: 0306-4522
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This study addressed the intraspinal release of immunoreactive calcitonin gene-related peptide in vivo during mech. stimulation of the normal joint and during the development of an acute exptl. inflammation in the knee joint in the anesthetized cat (spinalized) and rat (not spinalized).

Release was assessed using microprobes coated with antibody to calcitonin gene-related peptide; inhibition of binding of [125I]calcitonin gene-related peptide to these probes following insertion into the spinal cord is equated with intraspinal release of the endogenous (unlabeled) peptide. Probes inserted prior to inflammation showed marked basal release of immunoreactive calcitonin gene-related peptide in the dorsal horn with a maximum in the superficial dorsal horn in the absence of intentional stimulation. The pattern of binding of [125I]calcitonin gene-related peptide was not or only minimally changed by innocuous mech. stimuli (flexion of and innocuous pressure to the knee in the cat and innocuous pressure to the knee of the rat) but was significantly altered by elec. stimulation of the tibial nerve in the cat (sufficient to excite unmyelinated afferent fibers), indicating release of the peptide by the latter stimulus. During the first hours of the development of an exptl. inflammation in the knee joint induced by intra-articular injections of kaolin and carrageenan, the pattern of binding of [125I]calcitonin gene-related peptide changed. In the cat, the level of immunoreactive calcitonin gene-related peptide showed a persistent increase in the gray matter and up to the surface of the cord and release was slightly increased by innocuous stimuli. In the rat, increased levels of immunoreactive calcitonin gene-related peptide were mainly seen in the superficial and deep dorsal horn during innocuous pressure (this stimulus did not evoke release of the peptide prior to inflammation) and noxious pressure applied to the injected knee, whereas increased basal levels were only observed at later stages. These data show that the development of an acute exptl. inflammation in the joint is associated with an enhancement of the intraspinal release of immunoreactive calcitonin gene-related peptide. Since the changes in the release were noted at an early stage, within the first hours, they could contribute to the generation of inflammation-evoked changes of the responsiveness of spinal cord neurons and hence to the mechanisms inducing inflammatory **pain.**

L38 ANSWER 68 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:646333 HCAPLUS
DOCUMENT NUMBER: 121:246333
TITLE: Drug preparation based on ketoprofen for treatment of **pain**, inflammation, and/or fever in humans and animals
INVENTOR(S): **Geisslinger, Gerd**; Brune, Kay
PATENT ASSIGNEE(S): Germany
SOURCE: Ger., 8 pp.
CODEN: GWXXAW
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 4319438	C1	19940601	DE 1993-4319438	19930611 <--
WO 9428890	A1	19941222	WO 1994-EP1518	19940511 <--
W: AU, BG, BR, CA, CN, CZ, FI, HU, JP, KP, KR, NO, NZ, PL, RU, SK, UA, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9469272	A1	19950103	AU 1994-69272	19940511 <--

PRIORITY APPLN. INFO.: DE 1993-4319438 A 19930611
WO 1994-EP1518 W 19940511

AB The title prepns. contain the separated enantiomers of ketoprofen either as individual isomers or as a recombined mixture, where prepns. for treatment of **pain** contain 50-100% (R)-(-)-ketoprofen, which has very low

toxicity for the gastrointestinal tract, and prepns. for treatment of inflammation contain 50-100% (S)-(+)-ketoprofen. Ketoprofen may be present as an alkali metal, alkaline earth, ammonium, or amino acid salt, preferably as a lysine salt. In expts. with guinea pigs and gerbils, inversion of ketoprofen in vivo was <6%.

L38 ANSWER 69 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:525818 HCAPLUS
DOCUMENT NUMBER: 121:125818
TITLE: The involvement of excitatory amino acids and their receptors in the spinal processing of nociceptive input from the normal and inflamed knee joint in the rat
AUTHOR(S): **Schaible, Hans-Georg**; Neugebauer, Volker; Luecke, Thomas
CORPORATE SOURCE: Physiologisches Institut, Universitat Wurzburg, Wuerzburg, D-8700, Germany
SOURCE: NATO ASI Series, Series H: Cell Biology (**1994**), 79(CELLULAR MECHANISMS OF SENSORY PROCESSING), 195-215
CODEN: NASBE4; ISSN: 1010-8793
DOCUMENT TYPE: Journal
LANGUAGE: English
AB NMDA and non-NMDA receptors in afferent input from the knee joint were studied using microionophoresis of antagonists and agonists to examine antagonist interference with innocuous and noxious mech. stimuli applied to the normal knee joint and the effects of interference in the development of hyperexcitability of neurons in acute inflammation.

L38 ANSWER 70 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:427517 HCAPLUS
DOCUMENT NUMBER: 121:27517
TITLE: The involvement of N-methyl-D-aspartate (NMDA) and non-NMDA receptors in the responsiveness of rat spinal neurons with input from the chronically inflamed ankle
AUTHOR(S): Neugebauer, Volker; Luecke, Thomas; Grubb, Blair; **Schaible, Hans Georg**
CORPORATE SOURCE: Physiol. Inst., Univ. Wuerzburg, Wuerburg, 97070, Germany
SOURCE: Neuroscience Letters (**1994**), 170(2), 237-40
CODEN: NELED5; ISSN: 0304-3940
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Unilateral adjuvant inflammation was induced at the rat ankle 2 or 20 days before an evaluation. of the contribution of N-methyl-D-aspartate (NMDA) and non-NMDA receptors to the processing of nociceptive information by wide dynamic range neurons in the spinal cord. Microionophoretic application of either the NMDA receptor antagonists ketamine and DL-2-amino-5-phosphonovalerate (AP5) or the non-NMDA receptor antagonist 6-cyano-7-nitroquinoxaline 2,3-dione (CNQX) reduced the responses to innocuous and noxious mech. stimulation of the inflamed ankle. The pattern of these effects was comparable to that in rats with acute inflammation suggesting that non-NMDA and NMDA receptors are similarly involved in acute, prolonged acute and chronic inflammation-evoked activity.

L38 ANSWER 71 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:314994 HCAPLUS
DOCUMENT NUMBER: 120:314994
TITLE: Pure enantiomers of 2-arylpropionic acids: tools in

pain research and improved drugs in rheumatology
AUTHOR(S): Brune, Kay; **Geisslinger, Gerd**; Menzel-Soglowek, S.
CORPORATE SOURCE: Dep. Exp. Clin. Pharmacol. Toxicol., Univ. Erlangen-Nuernberg, Erlangen, D-8520, Germany
SOURCE: Journal of Clinical Pharmacology (**1992**), 32(10), 944-52
CODEN: JCPCBR; ISSN: 0091-2700
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 62 refs. The mode of action of aspirin-like drugs in **pain** is widely referred to as inhibition of prostaglandin synthesis. Salicylic acid, however, at low doses, is an analgesic but not a potent anti-inflammatory agent. This "enigma" may be resolved by recent findings employing 2-arylpropionic acids. Pure enantiomers of these chiral drugs show a different pharmacodynamic and pharmacokinetic profile. Using pure enantiomers of flurbiprofen, ibuprofen, and ketoprofen, the authors could show that (1) R-enantiomers of these drugs are inverted to S-enantiomers to a different degree in different species, including humans, (2) the pharmacokinetic parameters of both pure enantiomers differ in a drug- and a species-specific manner, and (3) both enantiomers exert differential analgesic effects. It appears particularly interesting that R-flurbiprofen, for instance, which is not or only to a small extent inverted in humans and rats, is practically devoid of prostaglandin synthesis inhibition in vitro. Consequently, in line with current thinking, R-flurbiprofen is not toxic to the gastrointestinal tract and shows no anti-inflammatory effects. In contrast to current concepts, however, this enantiomer does exert analgesic activity in different models of **pain** and nociception. It is concluded that R-flurbiprofen and, possibly, other R-enantiomers of 2-arylpropionic acids may exert novel analgesic effects independently of peripheral prostaglandin synthesis inhibition in inflamed tissue.

L38 ANSWER 72 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:213869 HCAPLUS
DOCUMENT NUMBER: 120:213869
TITLE: Afferent and spinal mechanisms of joint **pain**
AUTHOR(S): **Schaible, Hans Georg**; Grubb, Blair D.
CORPORATE SOURCE: Physiol. Inst., Univ. Wuerzburg, Wuerzburg, D-97070, Germany
SOURCE: Pain (**1993**), 55(1), 5-54
CODEN: PAINDB; ISSN: 0304-3959
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with .apprx.440 refs. on afferent and spinal mechanisms of nociception in the joint and on the efferent effects exerted by articular nerves on the joint. The involvement of neuropeptides in the mechanisms of joint **pain** is also discussed.

L38 ANSWER 73 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:213650 HCAPLUS
DOCUMENT NUMBER: 120:213650
TITLE: Properties of afferent nerve fibers supplying the saphenous vein in the cat
AUTHOR(S): **Michaelis, M.**; Goeder, R.; Haebler, H. J.; Jaenig, W.
CORPORATE SOURCE: Physiol. Inst., Christian-Albrechts-Univ., Kiel, 24098, Germany
SOURCE: Journal of Physiology (Cambridge, United Kingdom) (

1994), 474(2), 233-43
CODEN: JPHYA7; ISSN: 0022-3751
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors examined the responses of primary afferent neurons supplying a vascularly isolated segment of the saphenou vein to mech. and chemical stimuli in anesthetized cats. Activity was recorded from centrally cut axons of afferent nerve fibers which were isolated from the saphenous nerve near its junction with the femoral nerve. A total of thirty units responded to one of these stimuli and twenty-three of them were activated by local mech. stimulation of the venous wall. Most receptive fields were circular spots. The response of the isolated venous segment to distension was tested in fifteen out of thirty units and eight out of fifteen were activated. Intravasal threshold pressures inducing discharges were in the range of 35-250 mmHg with a mean of 120 mmHg. Twenty-seven out of the thirty units were tested for both mechano- and chemo-sensitivity. Thirteen were classified as A fibers and fourteen as C fibers with conduction velocities of 5-30 m s-1 and less than 2.5 m s-1, resp. Twenty fibers (12/13 A, 8/14 C) were mechanosensitive. Two-thirds of the mechanosensitive A (8/12) and all of the mechanosensitive C fibers (8/8) responded to at least one of the chemical stimuli used: hypertonic saline, bradykinin (BK) or capsaicin. The remaining seven units (6 C, 1 A) were activated by injection of BK into the isolated venous segment but failed to respond to mech. stimuli. Six were found during five expts. in which BK was used as a search stimulus. Injection of bradykinin into the isolated venous segment repeatedly induced an increase in systemic blood pressure. The proportion of unmyelinated fibers responding to mech. stimulation of the venous segment was systematically examined in three expts. and amounted to about 1% of the unmyelinated afferents in the saphenous nerve. In conclusion, a small proportion of afferent nerve fibers in the saphenous nerve responds to presumably noxious mech. and/or chemical stimuli applied to the saphenous vein. These fibers, together with some chemospecific venous afferents, may be capable of encoding nociceptive information from the vein especially under pathol. conditions.

L38 ANSWER 74 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:124668 HCAPLUS
DOCUMENT NUMBER: 120:124668
TITLE: The clinically available NMDA receptor antagonist memantine is antinociceptive on rat spinal neurons
AUTHOR(S): Neugebauer, Volker; Kornhuber, Johannes; Luecke, Thomas; **Schaible, Hans-Georg**
CORPORATE SOURCE: Physiol. Inst., Univ. Wuerzburg, Wuerzburg, D-97070, Germany
SOURCE: NeuroReport (**1993**), 4(11), 1259-1262
CODEN: NERPEZ; ISSN: 0959-4965
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In anesthetized rats antinociceptive effects of the clin. available drug memantine, an NMDA (N-methyl-D-aspartate) antagonist in vitro, were evaluated using extracellular recordings from spinal neurons with knee joint input. Memantine (1-12 mg kg-1) was applied i.v. before (control animals) or after induction of an acute knee joint inflammation which rendered spinal neurons hyperexcitable. Memantine (2 mg kg-1, i.v.) selectively reduced the responses to iontophoretic application of NMDA close to the neuron but not those to AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid). In control animals memantine reduced the neurons' responses to noxious but not to innocuous pressure on the knee. In rats with acute arthritis memantine reduced the responses to noxious and innocuous pressure. Thus memantine may be useful for the

treatment of **pain** states.

L38 ANSWER 75 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:595067 HCAPLUS
DOCUMENT NUMBER: 119:195067
TITLE: R-Flurbiprofen: Isomeric ballast or active entity of the racemic compound?
AUTHOR(S): **Geisslinger, G.**; Menzel-Soglowek, S.; Beck, W. S.; Brune, K.
CORPORATE SOURCE: Dep. Exp. Clin. Pharmacol. Toxicol., Univ. Erlangen-Nurnberg, Erlangen, D-8520, Germany
SOURCE: Agents and Actions Supplements (**1993**), 44(Variability in Response to Anti-Rheumatic Drugs), 31-6
CODEN: AASUDJ; ISSN: 0379-0363
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The enantioselective pharmacokinetic behavior of the flurbiprofen enantiomers was investigated following administration of optically pure R- or S-flurbiprofen to various species. Only negligible inversion (<5 %) of flurbiprofen occurred in the rat and in man. Consequently, pharmacodynamic expts. evaluating **pain** and inflammation as parameters have been carried out enantioselectively for both flurbiprofen enantiomers in the rat. R-flurbiprofen, which is not an inhibitor of prostaglandin synthesis in vitro, had only marginal anti-inflammatory effects as defined by the carrageenan edema of the rat paw in contrast to the S-enantiomer. In contrast, to S-flurbiprofen, R-flurbiprofen caused only marginal mucosal damage in the GI-tract. Both enantiomers, however, were of similar potency as antinociceptive drugs in the rat Randall-Selitto assay following the injection of interleukin-1 or baker's yeast. Using the pure enantiomers of flurbiprofen it appears to establish a more specific drug treatment: the R-enantiomer in occasional **pain**, the S-enantiomer in rheumatic disorders.

L38 ANSWER 76 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:532139 HCAPLUS
DOCUMENT NUMBER: 119:132139
TITLE: Differential effects of N-methyl-D-aspartate (NMDA) and non-NMDA receptor antagonists on the responses of rat spinal neurons with joint input
AUTHOR(S): Neugebauer, Volker; Luecke, Thomas; **Schaible, Hans Georg**
CORPORATE SOURCE: Physiol. Inst., Univ. Wuerzburg, Wuerzburg, Germany
SOURCE: Neuroscience Letters (**1993**), 155(1), 29-32
CODEN: NELED5; ISSN: 0304-3940
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In anesthetized rats the involvement of N-methyl-D-aspartate (NMDA) and non-NMDA receptors in the processing of innocuous and noxious sensory inflow from joints was assessed in 27 spinal dorsal horn neurons. Microiontophoretic application of either the NMDA antagonists ketamine and D,L-amino-5-phosphovalerate (AP5) or the non-NMDA antagonist 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) reduced the responses to noxious compression of the knee and ankle joint. By contrast, the responses to innocuous pressure were consistently reduced by CNQX but only exceptionally by NMDA antagonists. Therefore non-NMDA receptors are involved in the processing of innocuous and noxious mech. stimuli applied to the normal joint, whereas NMDA receptors are activated mainly by nociceptive input.

L38 ANSWER 77 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:469624 HCAPLUS
DOCUMENT NUMBER: 119:69624
TITLE: Peripheral nerve injury triggers noradrenergic sprouting within dorsal root ganglia
AUTHOR(S): McLachlan, Elspeth M.; Janig, Wilfrid; Devor, Marshall; **Michaelis, Martin**
CORPORATE SOURCE: Dep. Physiol. Pharmacol., Univ. Queensland, 4072, Australia
SOURCE: Nature (London, United Kingdom) (**1993**), 363(6429), 543-6
CODEN: NATUAS; ISSN: 0028-0836
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In humans, trauma to a peripheral nerve may be followed by chronic **pain** syndromes which are only relieved by blockade of the effects of sympathetic impulse traffic. It is presumed that, after the lesions, noradrenaline released by activity of sympathetic postganglionic axons excites primary afferent neurons by activating α-adrenoceptors, generating signals that enter the '**pain** pathways' of the central nervous system. The site of coupling is unclear. In some patients local anesthesia of the relevant peripheral nerve does not alleviate **pain**, implying that ectopic impulses arise either within the central nervous system, or in proximal parts of the primary afferent neurons. In exptl. lesioned rats, activity can originate within the dorsal root ganglia. The authors report that, after sciatic nerve ligation, noradrenergic perivascular axons in rats sprout into dorsal root ganglia and form basket-like structures around large-diameter axotomized sensory neurons; sympathetic stimulation can activate such neurons repetitively. These unusual connections provide a possible origin for abnormal discharge following peripheral nerve damage. Further, in contrast to the sprouting of intact nerve terminals into nearby denervated effector tissues in skin, muscle, sympathetic ganglia and sweat glands, the axons sprout into a target which has not been partially denervated.

L38 ANSWER 78 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:182687 HCAPLUS
DOCUMENT NUMBER: 118:182687
TITLE: Rapid determination of methadone in plasma, cerebrospinal fluid, and urine by gas chromatography and its application to routine drug monitoring
AUTHOR(S): Schmidt, Norbert; Sittl, Reinhard; Brune, Kay; **Geisslinger, Gerd**
CORPORATE SOURCE: Dep. Exp., Univ. Erlangen-Nuernberg, Erlangen, D-8520, Germany
SOURCE: Pharmaceutical Research (**1993**), 10(3), 441-4
CODEN: PHREEB; ISSN: 0724-8741
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Determination of methadone (MET) in biol. fluids can serve to adjust dosages in patients suffering from cancer **pain** or participating in methadone maintenance programs. We developed a gas chromatog. assay using nitrogen-phosphorus detection. The method involves a single-step extraction from alkalized plasma, cerebrospinal fluid, or urine into n-hexane-isoamylalc. (99:1, volume/volume). Dextropropoxyphene was used as internal standard Separation was achieved with a silica SE-52-CB column (13 m + 0.25-mm I.D.). The method was validated for the determination of MET in plasma, urine, and cerebrospinal fluid with a quantification limit of 0.5 ng/mL. The coeffs. of variation for within-day and between-day precisions were within 10.2 and 14.1%, resp. Approx. 100 samples can be analyzed by

one person in the course of a working day, making the method applicable to routine drug monitoring. The method was demonstrated to be sensitive and accurate for pharmacokinetic studies in plasma, urine, or cerebrospinal fluid.

L38 ANSWER 79 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1992:605792 HCAPLUS
DOCUMENT NUMBER: 117:205792
TITLE: Inflammatory mediators and nociception in the joint: excitation and sensitization of slowly conducting afferent fibers of cat's knee by prostaglandin I2
AUTHOR(S): Schepelmann, K.; Messlinger, K.; **Schaible, H. G.**; Schmidt, R. F.
CORPORATE SOURCE: Physiol. Inst., Univ. Wuerzburg, Wuerzburg, D-8700, Germany
SOURCE: Neuroscience (Oxford, United Kingdom) (**1992**), 50(1), 237-47
CODEN: NRSCDN; ISSN: 0306-4522
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of PGI2 on the discharge properties of fine articular afferents (group III and group IV fibers) in the cat were examined by extracellular recordings from single units dissected from the medial articular nerve of the knee joint. PGI2 was applied intra-arterially close to the joint in doses of 0.3-30 μg/0.3 mL bolus injection, and its effects on the spontaneous activity as well as on discharges evoked by mech. and chemical stimulation (bradykinin) were monitored. PGE2 was also applied and the effects of PGI2 and PGE2 on particular units were compared. An excitatory effect of PGI2 was observed in 49% of 37 group III and in 37% of 27 group IV units. A sensitization to passive movements of the joint occurred in 71% of 31 group III and 48% of 21 group IV units. Sixty-seven per cent of 32 units (groups III and IV) were both excited and sensitized by PGI2 to movements and 27% were sensitized but not excited. In 64% of 11 group III and 63% of 8 group IV units studied the responses to bradykinin were enhanced by PGI2. PGE2 had qual. similar effects as PGI2 but excited and sensitized a lower proportion of articular afferents. Forty-one percent of the units were sensitive to both prostaglandins but 26% of the fibers were only sensitive to PGI2. None of the units was exclusively sensitive to PGE2. In general, the excitatory and sensitizing effects of PGE2 had a longer duration than those exerted by PGI2. Thus, PGI2 increases the sensitivity to mech. stimuli as well as to chemical stimulation by bradykinin in the majority of articular group III and group IV fibers. Moreover, in a large proportion of articular afferents, PGI2 had an excitatory effect. Thus, PGI2 may be an inflammatory mediator which is important for inflammation-evoked activity in slowly conducting afferents and it may participate in the development of arthritic hyperalgesia and **pain.**

L38 ANSWER 80 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1992:120764 HCAPLUS
DOCUMENT NUMBER: 116:120764
TITLE: Differential effects of dipyrone, ibuprofen, and paracetamol on experimentally induced **pain** in man
AUTHOR(S): Forster, C.; Magerl, W.; Beck, A.; **Geisslinger, G.**; Gall, T.; Brune, K.; Handwerker, H. O.
CORPORATE SOURCE: Inst. Physiol. Biokybernet., Univ. Erlangen, Erlangen, W-8520, Germany
SOURCE: Agents and Actions (**1992**), 35(1-2), 112-21
CODEN: AGACBH; ISSN: 0065-4299

DOCUMENT TYPE: Journal
LANGUAGE: English
AB In a double-blind cross-over study on 22 healthy subjects, the analgesic efficacies of the antipyretic analgesic drugs ibuprofen, dipyrone and paracetamol were tested against placebo using a model of exptl. induced **pain.** To this purpose interdigital webs were pinched repeatedly for 2 min periods. The painfulness of these stimuli was assessed by the subjects on an electronically controlled visual analog scale at 10 s intervals. In addition to the subjective **pain** ratings the stimulus induced reflex diminution of the blood flow in the stimulated hand was measured with photoplethysmog. and laser Doppler flow anal. The flare response around the stimulated area was assessed with IR thermog. In this assay system ibuprofen and dipyrone, but not paracetamol, showed statistically significant analgesic effects by preventing hyperalgesia which is normally induced by the repeated stimulation of a skin site. This hypoalgesic effect was not related to the subjective impression of the subjects of the analgesic potency of the resp. drug. Sympathetic reflex vasoconstriction was not quant. related to the drug induced hypoalgesia. Ibuprofen and, to a minor extent, the other antipyretic analgesic drugs also diminished the stimulus induced flare reaction around the stimulated skin sites.

L38 ANSWER 81 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:199315 HCAPLUS
DOCUMENT NUMBER: 114:199315
TITLE: Aspirin-like drugs may block **pain** independently of prostaglandin synthesis inhibition
AUTHOR(S): Brune, K.; Beck, W. S.; **Geisslinger, G.**; Menzel-Soglowek, S.; Peskar, B. M.; Peskar, B. A.
CORPORATE SOURCE: Dep. Pharmacol. Toxicol., Univ. Erlangen-Nuernberg, Erlangen, D-8520, Germany
SOURCE: Experientia (**1991**), 47(3), 257-61
CODEN: EXPEAM; ISSN: 0014-4754
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Using flurbiprofen, a chiral anti-inflammatory and analgesic 2-arylpropionic acid derivative, the enantiomers of which are not converted to each other (less than 5%) in rats or man, evidence was obtained that prostaglandin synthesis inhibition is primarily mediating the antiinflammatory activity but prostaglandin synthesis, independent mechanisms contribute to the analgesic effects. Thus, the S-form inhibited prostaglandin synthesis, inflammation and nociception in rats. The R-form had much less effect on prostaglandin synthesis and did not affect inflammation. It did, however, block nociception in rats almost as potently as the S-form. S-Flurbiprofen, in contrast to the R-form, was clearly ulcerogenic in the gastrointestinal mucosa. These results indicate addnl. mol. mechanisms of analgesia and suggest the use of R-arylpropionic acids as analgesics.

L38 ANSWER 82 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:21591 HCAPLUS
DOCUMENT NUMBER: 114:21591
TITLE: Capsaicin inhibits responses of fine afferents from the knee joint of the cat to mechanical and chemical stimuli
AUTHOR(S): He, X.; Schepelmann, K.; **Schaible, H. G.**; Schmidt, R. F.
CORPORATE SOURCE: Physiol. Inst., Univ. Wuerzburg, Wuerzburg, D-8700, Germany
SOURCE: Brain Research (**1990**), 530(1), 147-50

CODEN: BRREAP; ISSN: 0006-8993
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In adult anesthetized cats the effects of capsaicin were studied on the responses of single slowly conducting afferents of the knee joint to mech. and chemical stimuli (bradykinin). An intra-arterial bolus injection of capsaicin into the joint reduced or abolished the responses to passive movements of the joint in 8 of 19 afferents and the responses to intra-arterially administered bradykinin in 10 of 11 units. Capsaicin was usually effective at 10-4-10-5M. The inhibition was predominantly observed in nociceptive afferents, whereas most low-threshold units were not desensitized.

L38 ANSWER 83 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1990:49443 HCAPLUS
DOCUMENT NUMBER: 112:49443
TITLE: Sensitization of articular afferents to mechanical stimuli by bradykinin
AUTHOR(S): Neugebauer, V.; **Schaible, H. G.**; Schmidt, R. F.
CORPORATE SOURCE: Physiol. Inst., Univ. Wuerzburg, Wuerzburg, D-8700, Fed. Rep. Ger.
SOURCE: Pfluegers Archiv (**1989**), 415(3), 330-5
CODEN: PFLABK; ISSN: 0031-6768
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Thin myelinated and unmyelinated articular afferents of the medial articular nerve of the knee joint were recorded in cats anesthetized with α-chloralose. Bradykinin was injected intra-arterially close to the knee, alone and in combination with PGE2, and changes of the responses of single afferents to movements of the knee were monitored. Bradykinin changed the mechanosensitivity in 20 of 28 afferents inducing movement sensitivity in initially unresponsive units, lowering the threshold for movements in high-threshold afferents and(or) enhancing pre-existing responses to innocuous and(or) noxious joint movements in low and high threshold units. The application of PGE2 and bradykinin within a short interval sensitized the majority of these afferents, and in .apprx.50% of the afferents the effect of the combination was superior to those induced by the single substances. Evidently, the inflammatory mediator bradykinin is able to sensitize articular afferents for movement stimuli and PGE2 may enhance this effect. It is suggested that in arthritis inflammatory mediators act synergistically in the initiation and stabilization of the increased mechanosensitivity of slowly conducting articular afferents.

L38 ANSWER 84 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1989:540370 HCAPLUS
DOCUMENT NUMBER: 111:140370
TITLE: Therapeutically relevant differences in the pharmacokinetic and pharmaceutical behavior of ibuprofen lysinate as compared to ibuprofen acid
AUTHOR(S): **Geisslinger, G.**; Dietzel, K.; Bezler, H.; Nuernberg, B.; Brune, K.
CORPORATE SOURCE: Dep. Pharmacol. Toxicol., Univ. Erlangen-Nuremberg, Erlangen, D-8520, Fed. Rep. Ger.
SOURCE: International Journal of Clinical Pharmacology, Therapy and Toxicology (**1989**), 27(7), 324-8
CODEN: IJCPB5; ISSN: 0300-9718
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The pharmacokinetic properties of ibuprofen (orally) given either as a

lysine salt or as acid to young, healthy male volunteers were investigated. Ibuprofen lysinate, administered after overnight fasting, produced peak plasma concns. significantly earlier and higher than ibuprofen acid. A similar difference was observed when the drugs were given following a standardized breakfast. Under these conditions the lag-time was significantly shorter for the lysine salt than for the acid. The pharmacokinetic differences are likely to result from the faster dissoln. rate of ibuprofen lysinate. The administration of ibuprofen as lysine salt before meals may be advantageous if rapid and reliable onset of **pain** relief is required.

L38 ANSWER 85 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1987:12126 HCAPLUS
DOCUMENT NUMBER: 106:12126
TITLE: Discharge characteristics of receptors with fine afferents from normal and inflamed joints: influence of analgesics and prostaglandins
AUTHOR(S): **Schaible, H. G.**; Schmidt, R. F.
CORPORATE SOURCE: Physiol. Inst., Univ. Wuerzburg, Wuerzburg, D-8700, Fed. Rep. Ger.
SOURCE: Agents and Actions Supplements (**1986**), AAS 19(100 Years Pyrazolone Drugs), 99-117
CODEN: AASUDJ; ISSN: 0379-0363
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 27 refs. discussing mostly the authors' research on inflamed joint receptors in cats and humans and the influences of prostaglandins and non-steroidal anti-inflammatory drugs (pyrazolones).

L38 ANSWER 86 OF 86 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1986:86331 HCAPLUS
DOCUMENT NUMBER: 104:86331
TITLE: Effects of prostaglandins E1 and E2 on the mechanosensitivity of group III afferents from normal and inflamed cat knee joints
AUTHOR(S): Heppelmann, B.; **Schaible, H. G.**; Schmidt, R. F.
CORPORATE SOURCE: Physiol. Inst., Univ. Wuerzburg, Wuerzburg, D-8700, Fed. Rep. Ger.
SOURCE: Advances in Pain Research and Therapy (**1985**), 9(Proc. World Congr. Pain, 4th, 1984), 91-101
CODEN: APRTDE; ISSN: 0146-0722
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The resting and evoked activities of group III afferents from knee joints were excited by direct effects of PGE1 [745-65-3] and PGE2 [363-24-6], and the prostaglandins also had a sensitizing effect on the nerves. The actions of the prostaglandins resembled those seen during exptl. inflammation, although they were of a much lesser magnitude. In inflamed tissue, prostaglandin injections induced much more powerful and long-lasting activation and sensitization of the group III afferents. The direct excitatory and the sensitizing actions did not always appear together in a given afferent unit, suggesting the involvement of independent processes in mediating there effects.

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